Cognitive and facial emotion processing abnormalities among children at-risk for schizophrenia
Candidate targets for early identification?

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Cognitive and facial emotion processing abnormalities among children at-risk for schizophrenia: Candidate targets for early identification?

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Abstract

Adults with schizophrenia are characterised by widespread cognitive and emotion dysfunctions. The neurodevelopmental hypothesis of schizophrenia posits that these abnormalities may precede the onset of overt clinical symptoms of illness, with progressive deterioration as individuals approach and transition to first-episode psychosis. The present thesis explored differences in cognitive performance and motor function in the childhood and adolescence of individuals who subsequently developed schizophrenia compared to those who did not, and examined cognitive and facial emotion processing abnormalities among children at-risk for schizophrenia and schizophrenia spectrum disorders. The findings presented in Chapter Four indicate that lower IQ and motor dysfunction, but not poor scholastic achievement, precede the prodromal phase of schizophrenia. Chapter Six provides evidence that at age 9 to 12 years, children presenting with a triad of antecedents of schizophrenia and children with a high familial loading for the disorder displayed diverse cognitive impairments. The results of Chapter Seven indicate that youth presenting with a triad of antecedents of schizophrenia and youth with a positive family history of the disorder exhibit some cognitive deficits that remain stable from 9 to 15 years, some deficits that increase with age, and other early deficits that show recuperation towards levels of typically developing children by 15 years. Finally, Chapter Nine demonstrates that children presenting with multiple antecedents of schizophrenia are characterised by poor facial emotion processing abilities. The findings of the present thesis indicate that children presenting with antecedents of schizophrenia display similar cognitive and facial emotion processing abnormalities to adults with schizophrenia and children with a positive family history of the disorder. However, only longitudinal follow-up of the children examined in the present thesis will establish the extent to which the triad of multiple antecedents is predictive of later psychotic or non-psychotic disorders.

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List of Abbreviations

Abbreviation	Meaning
ANCOVA	Analysis of Variance
ANOVA	Analysis of Covariance
ASz	A triad of antecedents of schizophrenia
ASz-no	Children presenting with a triad of antecedents who completed school screening questionnaires but did not supply contact information to participant in further research
BS	Basic Symptoms
CHADS	Child Health and Development Study
CHR	Clinical High-Risk
D-KEFS	Delis-Kaplan Executive Function System
DSST	Digit Symbol Substitution Task
EF	Executive Function
ER40	Emotion Recognition Task
ERP	Event-related Potential
FEP	First-Episode Psychosis
FER	Face Emotion Recognition
FHx	A first-and/or-second degree family member with schizophrenia
FHx^{H}	One first- or two second-degree relatives with schizophrenia
FHX^{L}	One second-degree relative with schizophrenia
FIGS	Family Interview for Genetic Studies
FU24	24 month follow-up
FU48	48 month follow-up
IQ	General Intelligence
PLEs	Psychotic-like experiences
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SES	Socio-economic Status
SSD	Schizophrenia Spectrum Disorders (inc: schizoaffective disorder and schizophreniform disorder)
TD	Typically-developing children with no antecedents of schizophrenia nor a family history of the disorder
TD-no	Typically-developing children who completed school screening questionnaires but did not supply contact information to participant in further research
UHR	Ultra High-Risk
WASI	Wechsler Abbreviated Scale of Intelligence
WIAT-II-UK	Wechsler Individual Achievement Test
WRAML2	Wide Range Assessment of Learning and Memory

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Statement of contribution to thesis

The analyses and interpretations presented in this thesis represent the work of the author, developed in discussion with my PhD supervisors, Dr Kristin Laurens and Professor Sheilagh Hodgins. The body of research comprising the thesis was conducted in collaboration with many others whose specific contributions are acknowledged following.

The thesis presents a subset of the data collected within a longitudinal research project, the London Child Health and Development Study (CHADS), which has been conducted at the Institute of Psychiatry, King's College London, since pilot work commenced in 2004. The CHADS project was designed by Dr Laurens and Professors Hodgins, Robin Murray, and Eric Taylor. Expert academic and clinical input to the study was also received from Professors Barbara Maughan, Michael Rutter, Robin Morris, Carmine Pariante, and Dr Brian Jacobs.

Dr Laurens and Professor Morris selected the neuropsychological test battery featured in this thesis, and Dr Laurens and I initiated collaboration with Drs Monica Calkins and Christian Kohler to select the computerised facial emotion recognition task. With my fellow PhD student Alexis Cullen, I was responsible for collection of the cognitive assessments at each phase of the research study. I also collected, and supervised undergraduate psychology students in the collection of, the facial emotion recognition data. I performed the data entry and analysis of these data, conducted the meta-analysis presented in chapter 4, and wrote this thesis under the supervision of Dr Laurens and Professor Hodgins. I gratefully acknowledge the contribution of additional co-authors to the revision of the drafts of publications based on the work presented in chapters 4 (Cullen) and 9 (Calkins and Kohler).

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Introduction

Schizophrenia[1] is a severe mental disorder with an average life time risk of 0.7% (Saha *et al.*, 2005). It is characterised by serious disturbances as reflected in three categories of symptoms: positive symptoms (hallucinations, delusions and movement disorders); negative symptoms (absence of motivation and emotion, language deficits, general apathy and social dysfunctions); and cognitive symptoms (poor understanding of information, problems with attention and problems with memory). Adults with schizophrenia present with widespread, but variable, structural, functional, and neurochemical brain dysfunction (Tandon *et al.*, 2008a). The peak age of onset for schizophrenia is in late adolescence or early adulthood, with a male-female relative lifetime risk of approximately 4:1 (Aleman *et al.*, 2003b, Mcgrath *et al.*, 2004). The prevalence of schizophrenia is higher among people of low socio-economic status than among those of higher socio-economic status and, within the UK, among individuals of African-Caribbean and black African ethnicity, as compared to those of white British ethnicity (Fearon *et al.*, 2006).

Nearly a quarter of individuals with schizophrenia fully recover after one or two acute psychotic episodes, half show partial recovery with remittent episodes, while among the remaining quarter the lifetime course of the disorder is chronic and debilitating (Hegarty *et al.*, 1994). In England during 2004/2005, societal costs of schizophrenia were estimated at £6.7 billion (Mangalore and Kapp, 2007). Moreover, diminished work capacity and an inability to sustain employment (Russinova *et al.*, 2002) create substantial poverty for people with the illness (Nordt *et al.*, 2012). In many

[1] Schizophrenia is currently classified as a psychotic disorder under the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders: DSM-5; American Psychiatric Association, 2013) and International Statistical Classification of Mental and Behavioural Disorders (ICD-10: World Health Organisation, 1992). The term "psychosis" is commonly used to describe the presence of symptoms of psychosis when more specific disorders are not, or cannot be, assessed. For example, at first presentation to a mental health service with an acute psychotic episode, it is often difficult to specify the specific disorder.

current services, treatment for schizophrenia is limited to antipsychotic medication, with many cases failing to comply. However, many additional treatments have been shown to have positive benefits for individuals with schizophrenia such as psychoeduction, cognitive therapy for psychosis, cognitive rehabilitation, employment training, and integrated treatments aimed at reducing misuse of alcohol and drugs (Leham *et al.*, 1993, Liu *et al.*, 2007, Morrison, 2009, Wykes *et al.*, 2011, Xia *et al.*, 2011).

Currently, there is no clear understanding of the causes of schizophrenia although the prevailing theory is that schizophrenia is a disorder of neurodevelopmental origin. The accumulated evidence suggests that multiple genes, each making a small contribution, initiate abnormal neural development that is further exacerbated by environmental factors from the foetal stage onwards (Rapoport *et al.*, 2012). In support of the neurodevelopmental hypotheses, considerable evidence shows that brain changes and cognitive, behavioural, and emotional dysfunctions precede illness onset (Niemi *et al.*, 2003, Welham *et al.*, 2009a, Woodberry *et al.*, 2008). A promising method for averting illness onset may be to identify vulnerable individuals well before the prodromal phase of schizophrenia based on the presence of these early risk factors for the disorder.

Aims and hypotheses

This thesis explored cognitive and facial emotion processing abnormalities among children at-risk for schizophrenia and schizophrenia spectrum disorders[2] (SSD). Previous investigations have focused on individuals with a positive family history of the disorder or help-seeking, symptomatic individuals meeting ultra-high risk (UHR) criteria for psychosis (i.e., either attenuated psychotic symptoms; brief, limited intermittent psychotic symptoms; or genetic risk plus functional decline). However,

[2] For the purposes of the thesis the term schizophrenia spectrum disorder includes schizophrenia, schizoaffective disorder, and schizophreniform disorder.

while behavioural-genetic studies concur in showing high heritability of schizophrenia and SSD (Tandon *et al.*, 2008a), a positive family history of schizophrenia identifies only a minority of individuals who develop the disorder. Strategies identifying individuals based on UHR criteria identify only help-seeking adolescents or young adults who may be at imminent risk of developing schizophrenia or SSD.

By contrast, prospective longitudinal studies of population cohorts and follow-back studies of adults with schizophrenia have identified multiple antecedents that distinguished cohort members who developed schizophrenia or SSD from those who did not. Recent efforts have been made to identify children and adolescents who may be at elevated risk for schizophrenia or SSD based on the presence of these known antecedents of the disorder (Kelleher and Cannon, 2011, Kelleher *et al.*, 2012b, Laurens *et al.*, 2007, Laurens *et al.*, 2011, Zammit *et al.*, in press). These novel approaches to defining at-risk status have the potential to further understanding of the development of schizophrenia or SSD (Cornblatt and Obuchowski, 1997). Moreover, the early identification of children presenting risk for schizophrenia, well prior to the typical age of illness onset in late adolescence/early adulthood, may offer the best prospect for early intervention to remediate difficulties that contribute to development of the illness.

Research indicates that impaired cognitive, motor, and emotion processing abnormalities in childhood may index vulnerability for schizophrenia (Matheson *et al.*, 2011). These deficits in childhood and early adolescence are potential targets for interventions that may modulate the development of the illness or reduce the extent of dysfunction among those who develop schizophrenia or SSD. The purpose of this thesis was to assess the utility of a novel strategy to identify children aged 9-12 years who

present with a triad of known antecedents[3] of schizophrenia (motor and/or speech delays, clinically relevant internalising and/or externalising problems, and psychotic-like experiences). The thesis explored whether these children exhibited the cognitive and facial emotion processing abnormalities that are present in adults with schizophrenia and that are also observed among youth at elevated risk for schizophrenia or SSD based on either family history or UHR criteria. The rationale and background of the specific aims of the thesis are addressed in more detail in the relevant chapters. Briefly, the aims of the thesis and the hypotheses of each study are described below:-

- To conduct a meta-analysis of differences in cognitive and motor performance in the childhood and adolescence of individuals who subsequently developed schizophrenia and in those who did not (Chapter Four).
    - We hypothesised that meta-analyses would show that cognitive and motor deficits are present prior to the prodromal phase of schizophrenia among youth who subsequently develop schizophrenia in adulthood.
- To determine whether children aged 9 to 12 years characterised by a triad of well-replicated antecedents of schizophrenia exhibit cognitive impairments relative to typically developing children, and similar to those exhibited by adults with schizophrenia and by adolescents and young adults seeking help for prodromal symptoms (Chapter Six).

[3] The triad of antecedents assessed via school screening questionnaires represent among the most replicated, predictive, and sensitive precursors of schizophrenia reported in prospective longitudinal population cohort studies and prospective investigations of offspring born to a parent with the disorder (Laurens *et a*l., 2007). Antecedents of schizophrenia may be expressed as premorbid deficits or deviations that might reflect early passive expression of pathology, or that may actively modify risk within an aetiological pathway (Matheson *et al*., 2011). At present, little is known about the proportion of children experiencing these antecedents who may go on to develop schizophrenia or SSD. Similarly, even less is known about the undoubtedly much larger proportion of children with these supposed antecedents who do not develop schizophrenia or SSD. Hence, for the purposes of the thesis, although the term antecedents is used, such variables are best understood as potential 'risk factors' for the later development of the disorder, and should not be assumed to invariably precede the disorder, as might be implied by the term antecedent (or premorbid abnormality).

- We hypothesised that children with antecedents of schizophrenia and children with a higher and lower familial loading for schizophrenia would be characterised by lower IQ and poorer scholastic achievement, memory, and executive function than typically developing children, but that the pattern of impairment might differ across the groups.

- To determine whether children aged 9 to 12 years with varying degrees of family loading for schizophrenia present cognitive impairments relative to typically developing children, whether these impairments vary by degree of family loading for schizophrenia, and whether these impairments are similar to those displayed by children of the same age characterised by a triad of well-replicated antecedents of schizophrenia (Chapter Six).
    - We hypothesised that children with a higher familial loading for schizophrenia would display greater neurocognitive impairment than children with lower familial loading for the disorder.
- To investigate whether IQ explains the cognitive deficits of children characterised by a triad of well-replicated antecedents of schizophrenia and children with affected relatives (Chapter Six).
    - We tested the hypothesis that specific cognitive impairments among children with antecedents of schizophrenia and children with a family history of schizophrenia would reflect a generalised cognitive (IQ) deficit.
- To investigate stability and change on multiple cognitive domains from late childhood into mid-adolescence among children characterised by a triad of well-replicated antecedents of schizophrenia and children with affected relatives (Chapter Seven).
    - We hypothesised that, between the ages of 9 and 15 years, children presenting with antecedents of schizophrenia and children with a positive

family history of schizophrenia or SSD, as compared to typically developing children, would exhibit differences in age-related rate of change in IQ, scholastic achievement, memory, working memory, and executive function.

- To determine whether children presenting with a triad of antecedents of schizophrenia exhibit difficulties in recognising emotions in the faces of others (Chapter Nine).
    - We tested the hypothesis that children with a triad of antecedents of schizophrenia would be less accurate than typically developing peers in identifying emotions in facial expressions, and that they would more often mislabel faces displaying no emotion (neutral expressions) with other emotional expressions.

Outline of the thesis

The thesis comprises ten Chapters and has been divided into two sections. Section one focuses on cognition and section two on facial emotion processing.

- Chapter One outlines study designs that explore antecedents of schizophrenia or SSD.
- Chapter Two describes the rationale for adopting a novel strategy to identify children at elevated risk for schizophrenia or SSD as implemented within the Child Health Development Study (CHADS), from which the studies reported in this thesis derive.
- Chapter Three outlines the general methodology adopted within the CHADS project.

Section one: Cognition

- Chapter Four (section one) presents the results of a meta-analyses examining IQ, academic achievement, and motor function among children and young

adolescents (aged ≤ 16 years and aged ≤ 13 years), comparing those who subsequently developed schizophrenia or SSD and those who did not.

- Chapter Five (section one) provides a comprehensive literature review of cognitive dysfunctions among individuals at elevated risk for the development of schizophrenia based on early identification strategies described in Chapter one.
- Chapter Six (section one) describes a cross-sectional study of cognitive function among children aged 9 to 12 years old presenting with multiple antecedents of schizophrenia and children with a high and low familial loading for the disorder compared to typically developing children.
- Chapter Seven (section one) extends the findings of the previous Chapter by presenting the results of longitudinal repeated measures mixed modelling analyses examining the developmental course of cognitive function from childhood into adolescence among youth presenting with antecedents of schizophrenia and youth with affected relatives.

Section Two: Facial Emotion Processing

- Chapter Eight (section two) provides a literature review of facial emotional processing abnormalities among individuals at elevated risk for the development of schizophrenia based on early identification strategies described in Chapter One.
- Chapter nine describes findings from a cross-sectional study of facial emotion processing abnormalities comparing children with multiple antecedents of schizophrenia to typically developing children aged 9 to 14 years.
- Chapter Ten presents a brief summary of results of study chapters, implications and potential application of thesis findings, and strengths and limitations of the research.

Publications arising from thesis

Work from this thesis has, to date, generated two published journal papers, one accepted journal paper, one manuscript in preparation, two published abstracts, and an oral and a poster presentation at International conferences. Copies of the published journal articles are included in appendices I and II. I have also been a co-author on two other published journal papers derived from the CHADS project, which are not included here, as they are not directly relevant to this thesis. The work of this thesis is original and can be briefly summarised as:

- A meta-analysis showed that lower IQ and motor dysfunction, but not poor scholastic achievement, preceded the prodromal phase of schizophrenia (Chapter Four).
- At age 9 to 12 years, children presenting with multiple antecedents of schizophrenia and children with a positive family history of the disorder displayed diverse cognitive impairments (Chapter Six).
- Children with a higher familial loading for schizophrenia are more cognitively impaired than children with a lower familial loading for the disorder (Chapter Six).
- To some extent, observed cognitive deficits among children presenting with multiple antecedents of schizophrenia and children with a positive family history of the disorder reflect group differences in IQ (Chapter Six).
- Youth presenting with multiple antecedents of schizophrenia and youth with a positive family history of the disorder exhibit some cognitive deficits that remain stable from 9 to 15 years, some deficits that increase with age, and other deficits that show recuperation towards levels of typically developing children by 15 years (Chapter Seven).

- Children presenting with multiple antecedents of schizophrenia are characterised by poorer facial emotion processing abilities (Chapter Nine).

Chapter 1 Identification of the antecedents of schizophrenia

Aims of the chapter

This chapter reviews different types of investigations that aim to identify the antecedents of schizophrenia and SSD.

1.1 Retrospective studies of adults with schizophrenia

One strategy for collecting information on childhood antecedents of schizophrenia is to question adults with schizophrenia and/or their family members. While such information is subjective and biased by the development of illness, it can be supplemented by objective evidence, such as records of academic performance, IQ tests, reports of behaviour from classroom teachers, and in some countries records of contacts with health services, social services, and the criminal justice system. These studies are helpful for identifying factors of risk or protection particularly when the outcome (e.g., schizophrenia) has a relatively rare incidence in the general population. Evidence from retrospective studies of adults with schizophrenia has identified low IQ, poor scholastic achievement, motor dysfunction, and social, emotional, and behavioural difficulties (Albee *et al.*, 1964, Amminger *et al.*, 1999, Ang and Tan, 2004, Bilder *et al.*, 2006, Fuller *et al.*, 2002, Kim-Cohen *et al.*, 2003, Offord, 1974, Roff and Fultz, 2003, Walker *et al.*, 1994, Watt and Lubensky, 1976).

1.2 Prospective longitudinal studies of population cohorts

Prospective longitudinal studies follow population cohorts of individuals usually from early childhood to adulthood. Individuals are assessed repeatedly through the follow-up period. In adulthood, the childhood characteristics of those who did and who do not develop schizophrenia or SSD are compared. Prospective, longitudinal investigations of population cohorts provide the most robust evidence on the childhood and adolescent factors that distinguish individuals who develop schizophrenia and SSD.

However, given the low prevalence rate of schizophrenia in the general population (Saha *et al.*, 2005), prospective longitudinal studies require large cohorts and low rates of subject attrition over time in order to have sufficient numbers of cohort members who develop schizophrenia or SSD. However, sample attrition rates are often high, around 30% to 70% (Gustavson *et al.*, 2012). Therefore, participant dropout from longitudinal population-based studies can be problematic when the prevalence rate of the disorder is low (Guterman, 2004). Furthermore, such investigations are expensive and time-consuming to conduct. Similar to retrospective studies of adults with schizophrenia, evidence from these investigations indicates that children and adolescents who develop schizophrenia or SSD in adulthood are characterised by social, emotional, and behavioural problems, intellectual and cognitive impairments, and speech, language, and motor abnormalities, and psychotic-like experiences (PLEs) (Matheson *et al.*, 2011). Importantly, measures of childhood factors assessed retrospectively and prospectively have been shown to be similarly related to adult psychopathology (Scott *et al.*, 2012).

1.3 Military conscription studies

A further strategy for identifying antecedents of schizophrenia is through military conscript studies. These studies utilise data taken on entry to the army when individuals are in late adolescence/early adulthood which is then linked to later hospital records. Evidence from Swedish, Israeli, and Finnish military cohorts indicates that poor cognitive ability on entry into the army is predictive of later schizophrenia and other psychiatric diisorders (David *et al.*, 1997, David *et al.*, 2008, Davidson *et al.*, 1999, Gunnell *et al.*, 2002, Reichenberg *et al.*, 2002, Tiihonen *et al.*, 2005, Zammit *et al.*, 2004). Strengths of these studies include large sample sizes and linkage to hospital records. However, these studies only include males assessed in early adulthood and offer little information on the earliest premorbid characteristics of both males and

females who subsequently develop schizophrenia. More recently, MacCabe and colleagues examined verbal, spatial, and inductive ability of 10, 717 Swedish males at 13 years and equivalent tests at age 18 years at army conscription (Maccabe *et al.*, 2013). A decline in cognitive performance between 13 and 18 years particularly in verbal ability was associated with increased risk for psychosis

1.4 Family history of schizophrenia

Prospective, longitudinal studies following the development of children of parents with schizophrenia were first established in the 1960's. Prior to the recent studies of population cohorts described above, these so called "high risk" studies were the principal sources of information on the childhood antecedents of schizophrenia. The purpose of these studies was to study the aetiology of schizophrenia by investigating those at elevated risk for it; namely by genetic relatedness (Niemi *et al.*, 2003).

Behavioural-genetic studies concur in showing high heritability of schizophrenia and SSD (Tandon *et al.*, 2008a). Further, the risk of schizophrenia increases with degree of genetic relatedness within families (Gottesman and Sheilds, 1982) such that first-degree relatives of individuals with schizophrenia have a life-time risk 10 times greater than the general population (Kendler *et al.*, 1995). The risk among first-degree relatives ranges from 5.6% in parents of patients, to 12% for children with a parent with the disorder, up to 46% if a child has two affected parents (Gottesman and Sheilds, 1982), and a further 20% developing the disorder within the schizophrenia spectrum (Cannon *et al.*, 1990).

Prospective longitudinal studies of offspring of adults with schizophrenia include repeated assessments through childhood and adolescence of a broad range of biological, cognitive, environmental, and psychosocial factors. These assessments were more thorough than those of much larger population cohorts followed prospectively. Results

from these early “high-risk” studies indicated that early precursors to schizophrenia were the presence of more obstetric complications and neurobehavioral abnormalities, negative parenting styles, and maternal exposure to influenza, whilst during childhood and adolescence later schizophrenia was associated with cognitive and motor dysfunctions and social, emotional, and behavioural difficulties (Erlenmeyer-Kimling and Cornblatt, 1987, Fish, 1987, Goodman, 1987, Marcus *et al.*, 1987, Mednick *et al.*, 1971).

A confounding factor of these studies was that in addition to possible genetic risk for SSD, the children were being raised by an ill parent. To address this issue, a number of studies prospectively followed children of a parent with schizophrenia who were adopted away in early childhood and raised by healthy parents. These investigations have provided additional support for the contribution of both genetic and environmental factors to schizophrenia. The prevalence of schizophrenia was found to be higher among individuals born to a parent with schizophrenia and adopted away to healthy parents than among adoptees of healthy parents adopted away to healthy parents (Heston, 1966, Rosenthal *et al.*, 1971, Tienari *et al.*, 2004). Tienari and colleagues found that children born to a parent with schizophrenia and adopted into a positive family environment were less likely to develop schizophrenia than those adopted into negative family environments (Tienari *et al.*, 2004).

However, results of studies of offspring with an affected parent showed that abnormalities identified as ‘markers’ of risk were not always specific to schizophrenia (Niemi *et al.*, 2003), nor were they consistently replicated across studies. Further, approximately two-thirds of individuals with schizophrenia have neither an affected first -or second-degree relative and, by contrast, 87% of children who have a parent with schizophrenia or SSD will not develop either of these disorders (Gottesman and Erlenmeyer-Kimling, 2001). Those who do not develop schizophrenia or SSD are also

at increased risk to develop another mental disorder. For example, in a study of 1.74 million people born in Denmark 1955-1991, schizophrenia was strongly associated with schizophrenia and related disorders among first degree relatives. However, almost any other mental disorder among first-degree relatives increased the individual's risk of schizophrenia. The population attributable risk associated with any mental disorder among relatives was 27.1% while the presence of schizophrenia among relatives only accounted for 6.0%. (Mortensen *et al.*, 2010). Thus, a positive family history of schizophrenia identifies children who show elevated risk for schizophrenia and an even higher risk for other mental disorders (Mortensen *et al.*, 2010).

More recent studies have also examined other unaffected first-degree relatives (i.e., siblings and parents) and second-degree relatives (i.e., uncle, aunt, niece, and nephew) of adults with schizophrenia. Study samples vary in age and thereby in risk. Characteristics shared by non-ill relatives who have passed through the typical age period of peak illness onset (usually > 30 years) and their affected relative that distinguish them from healthy individuals are presumed to be heritable and to reflect vulnerability for schizophrenia (Agnew-Blais and Seidman, 2013). Most of the abnormalities shared by non-ill and ill relatives and not by healthy individuals is thought to manifest as non-psychotic abnormalities (Weinberger, 2002). In contrast, the prospective assessment of young first or second-degree relatives ($\leq$30 years) of individuals with schizophrenia on a broad range of biological, cognitive, environmental, and psychosocial measures enables the investigation of early life events and provides information on causal pathways to schizophrenia and other psychotic illnesses. Utilising mainly cross-sectional designs, evidence from these studies has by and large confirmed the findings from earlier, prospective longitudinal studies of offspring of a parent with schizophrenia and contributed new data on cognitive and emotional dysfunctions among

young unaffected relatives with a family history of schizophrenia (Agnew-Blais and Seidman, 2013, Schenkel and Silverstein, 2004).

A promising avenue of further investigation may be the use of multivariate prediction models in studies of youth with affected relatives. The inclusion of other risk factors for schizophrenia in conjunction with a positive family history may be more effective in predicting schizophrenia than a family history alone. Indeed, recent work has reported that high-levels of psychosis-proneness or schizoptypy, in addition to having a first-degree or second-degree relative with the disorder, were predictive of conversion to schizophrenia (Shah *et al.*, 2012, Tandon *et al.*, 2012).

1.5 Symptomatic, help-seeking individuals

The onset of schizophrenia is usually preceded by a 'prodromal' phase that is characterised by nonspecific changes in behaviour, emotional state, and/or cognitive state, and signs of deterioration in functioning (Yung *et al.*, 2004). The early signs/symptoms of this phase of illness include social withdrawal, odd or uncharacteristic behaviour, disturbed communication and affect, unusual ideation and perceptual experiences, poor personal hygiene, and reduced interest and motivation. Individuals often present such symptoms/abnormalities from approximately five years prior to illness onset (Hafner *et al.*, 1995).

Different sets of criteria have been used to identify individuals presenting to clinical services with prodromal features. Ultra-High Risk (UHR: Yung, 2003, Yung and Mcgorry, 1996a) or Clinical High-Risk (CHR: Mcglashan *et al.*, 2001, Miller *et al.*, 1999) criteria include a diagnosis of attenuated psychotic symptoms, brief limited intermittent transient psychotic symptoms (that is, full threshold positive psychotic symptoms), or a substantial drop in social and role functioning in conjunction with a family history of psychosis or schizotypal personality disorder. Another approach uses

self-reports of “basic symptoms”, including disturbances in thought, language, perception, tolerance to stress, and social-emotional reactivity to identify at-risk individuals (Klosterkötter *et al.*, 1996, Klosterkötter *et al.*, 2001).

Table 1 below provides an overview of screening instruments and criteria that have been used to identify individuals with prodromal symptoms. The UHR or Clinical High Risk criteria are thought to identify individuals who will transition to illness within one to two years. Older UHR studies reported rates of conversion to psychosis from 21% (Yung and Mcgorry, 1996b) to 54% within the first 12 months after identification (Miller *et al.*, 2002), but a more recent meta-analysis of studies of help-seeking individuals meeting UHR criteria reported lower, but increasing transition rates over time: 18% at six months, 22% after one year, 29% after two years, and 36% after three years (Fusar-Poli *et al.*, 2012a).

Table 1: Description of the instruments and criteria identifying symptomatic, help-seeking individuals

Term	Instruments?	Inclusion criteria
• Ultra high-risk (UHR) • At-risk mental state (ARMS) • Clinical high-risk (CHR)	• Comprehensive Assessment of At-Risk Mental state (CAARMS: Yung *et al.*, 1996)[a] • Structured Interview for Prodromal Syndromes/ Scale of Prodromal Symptoms (SIPS/SOPS: Miller *et al.*, 1999)[b, c]	• Attenuated psychotic symptoms (APS) e.g., unusual thought content, delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities, hallucinations, disorganised communication and odd behaviour/appearance • Brief limited intermittent psychotic symptoms (BLIPS) e.g., hallucinations, delusions or formal thought disorder (full threshold positive symptoms) • Genetic risk + recent functional deterioration: 1st/2nd degree relative with psychotic or schizotypal personality disorder AND a 30% or more reduction in score on Global Assessment of Functioning Scale (GAF).
Basic Symptoms	• Originally assessed by Bonn Scale for Assessment of Basic symptoms (BSABS: Gross *et al.*, 1987). • Schizophrenia Proneness Instrument Adult Version (SPI-A: (Schultze-Lutter *et al.*, 2007a) now used.	Basic symptoms comprise: attention difficulties; thought interference, pressure and blockage; disturbances of speech, abstract thinking; ideas of reference. Two subsets (Schultze-Lutter *et al.*, 2007b): • COPER: 1 or more out of 10 cognitive/perceptual basic symptoms of moderate severity (score > 3) in last 3 months with onset over one year • COGDIS: 2 or more out of 9 cognitive disturbances or moderate severity (score > 3) in last 3 months

Notes: [a] APS= Present for more than one week in past year for less than 5 years; BLIPS= duration less than one week with spontaneous remission, occurred within past year but not for longer than 5 years; and GRD=Decrease in global functioning maintained for at least a month but less than 5 years. [b] APS= Present for least once per week in past month with onset or worsening in past year; BLIPS= Onset in last three month for a minimum of one hour a day every approximately every week for past month: and GRD=Drop in global functioning in past month compared to one year ago. [c] The Recognition and Prevention programme (RAP) uses SIPS but has established further criteria with CHR+ identifying individuals based on APS and CHR- including attenuated negative symptoms only (Cornblatt *et al.*, 2003).

Although UHR, Clinical High Risk, and Basic Symptom criteria include similar clinical features (Fusar-Poli *et al.*, 2013a), Basic Symptoms are present through disease progression while UHR/Clinical High Risk criteria identify features associated with transition to psychosis (Simon *et al.*, 2007). Thus, transition rates to psychosis differ for individuals identified using different criteria. Individuals meeting UHR or Clinical High Risk criteria only, present a transition rate of approximately 30%-35% within one to three years follow-up (Cannon *et al.*, 2008, Cornblatt *et al.*, 2003, Ruhrmann *et al.*, 2010b, Yung *et al.*, 2003), while 49.4% of youth displaying Basic Symptoms at baseline developed schizophrenia approximately five years later (Klosterkötter *et al.*, 2001). Therefore, Basic Symptoms may be better conceptualised as an "early prodromal state" with UHR or Clinical High Risk criteria identifying individuals in a "later" prodromal phase. Recently, investigations that identify individuals based on UHR or Clinical High Risk and Basic Symptom criteria indicate higher transition rates to psychosis than using either UHR, Clinical High Risk or Basic Symptoms criteria alone (Ruhrmann *et al.*, 2010b, Simon *et al.*, 2007). Consistent with the "early" and "late" models of the prodrome is the finding that individuals meeting UHR criteria who report either Attenuated Psychotic Symptoms or Brief Limited Intermittent Psychotic Symptoms are in a "later" phase of the prodrome as closer to transition over the short-term than individuals with a family history of psychosis who also report functional decline (Nelson *et al.*, 2011). UHR, Clinical High Risk and Basic Symptom criteria are herein collectively referred to as UHR.

1.5.1 Refining Ultra High- Risk strategies

At present, UHR strategies require further precision in order to identify only those individuals who will develop schizophrenia (Cannon *et al.*, 2008). Adding further risk criteria to those used in previous studies of help-seeking individuals may facilitate a

better and more individualised estimate of risk, but prediction is complicated by the non-specific psychopathology that precedes the onset of frank psychosis (Keshavan *et al.*, 2008). Multivariate prediction models aim to predict schizophrenia with a higher specificity and sensitivity than that afforded by UHR criteria. Yung and colleagues found that by adding either duration of symptoms, poor psycho-social functioning, depression or decreased attention to UHR criteria improved prediction (Yung *et al.*, 2004). A similar study reported that variables assessing odd beliefs/magical thinking, impaired role functioning, blunted or inappropriate affect, anhedonia, and auditory hallucinations were predictive of transition to psychosis with good sensitivity (84%) and specificity (86%) among UHR youth (Mason *et al.*, 2004).

More recently, studies examining clinical predictors of psychosis among samples of individuals meeting UHR criteria have reported that a family history of psychosis accompanied by functional decline, high unusual thought content, high suspiciousness/paranoia, poor social functioning, and a history of substance misuse increased the accuracy of prediction to between 68% and 80% compared to the 35% using UHR criteria alone. However, the sensitivity of this model for detecting those who developed schizophrenia was low (Cannon *et al.*, 2008). This finding was also replicated using three of the variables (unusual thought content, family history of psychosis with functional decline, and poor social functioning) in another sample of individuals meeting UHR criteria (Thompson *et al.*, 2011a). European investigations of individuals meeting UHR criteria have also shown increased predictive accuracy when adding the following variables: presence of psychotic-like experiences (PLEs), bizarre thinking, sleep disturbances, schizotypal personality disorder features, global functioning, and years of education (Ruhrmann *et al.*, 2010b), high suspiciousness, and anhedonia scores (Riecher-Rössler *et al.*, 2009). Further attempts have included other possible predictors of illness such as neurocognitive, neurobiological, and

neuroanatomical abnormalities, and have been successful in yielding higher transition rates than UHR criteria alone (Koutsouleris *et al.*, 2012, Koutsouleris *et al.*, 2009, Mechelli *et al.*, 2011, Riecher-Rössler *et al.*, 2009, Van Tricht *et al.*, 2011).

In addition to UHR symptoms, individuals meeting UHR criteria for psychosis particularly those who later transition to psychosis often present with comorbid psychopathology (anxiety, depression, and substance use disorders) , poor social and role functioning and widespread cognitive impairment (Cornblatt *et al.*, 2012, Correll *et al.*, 2010, Fusar-Poli *et al.*, 2013a). However, while investigations of individuals meeting UHR criteria successfully identify a proportion of individuals who develop psychosis, they can offer little information on the earliest premorbid stage of schizophrenia or SSD. Given that UHR individuals are help-seeking and already in young adulthood, at an age when prodromal symptoms often begin, it is not clear whether the presence of clinical symptoms, poor social and role functioning and cognitive impairment represent an early prodromal disease process or antecedents of schizophrenia. Further, while substantial proportions of help-seeking individuals meeting UHR criteria do transition to psychosis they are not representative of individuals who develop the disorder (Fusar-Poli *et al.*, 2013b).

1.5.2 A clinical staging approach to schizophrenia

A retrospective study of individuals experiencing their first-episode of psychosis (FEP), found that the onset of non-specific symptoms occurred, on average, eight years before first contact with mental health services, followed by onset of attenuated psychotic symptoms at four years, basic symptoms at three years, and psychotic symptoms two years prior to admission to hospital (Schultze-Lutter *et al.*, 2010). These findings suggest a slow progression through stages that begin with milder symptoms which are distinguishable from the later severe and debilitating features of illness. A clinical staging model has been proposed as a way of understanding the development of

schizophrenia (Keshavan *et al.*, 2011, Mcgorry *et al.*, 2008, Wood *et al.*, 2011). The stages are described in Table 2 below. UHR criteria identify individuals at "Stage Ib" or "Late, narrowly defined at-risk state", with subtle non-specific symptomology emerging prior to this at "Stage I", or an "Early, broadly defined at-risk state". The earliest premorbid stage (that is, before the "Early, broadly defined at-risk state") has not been fully characterised. However, as described above, evidence from prospective longitudinal studies of population cohorts and children of parents with schizophrenia indicates that children who later develop schizophrenia are characterised by abnormalities in motor and language function, disturbances in social, emotional and behavioural functioning, PLEs, and neuroanatomical abnormalities (Niemi *et al.*, 2003, Welham *et al.*, 2009a).

Table 2: Proposed staging models of schizophrenia

	Stage (Wood *et al.,* 2011)	Phase (Keshavan *et al.,* 2011)
Stage 0/Premorbid	Increased risk of psychotic or severe mood disorder. No symptoms currently	Stable cognitive, social or neuromotor deficits (no negative or positive symptoms)
Stage Ia/ "Early", broadly defined at-risk state	Mild or non-specific symptoms (neurocognitive deficit, PLEs associated with mild functional decline, mood/anxiety symptoms that lead to distress or help-seeking) and mild functional change or decline.	Mild positive, negative or general symptoms, cognitive deficits, and mild-moderate functional decline
Stage Ib/ "Late", or narrowly defined at-risk state	UHR: Moderate but subthreshold symptoms, with/without mild to moderate neurocognitive changes, comorbid substance abuse, and with functional decline.	Recently worsening attenuated positive symptoms or new onset fluctuating psychotic symptoms, marked functional decline
Stage II	Full threshold disorder with moderate-severe symptoms, neurocognitive deficits, and functional decline	Persistent or severe psychotic symptoms
Stage III	Incomplete remission or recurrence/relapse	Not specified
Stage IV	Severe, persistent, and unremitting illness as judged on symptoms and disability criteria	Not specified

1.6 Studies of children and adolescents reporting psychotic like-experiences

PLEs, or subclinical psychotic symptoms, in adult populations are relatively rare, with a median prevalence of ~8% (Nuevo *et al.*, 2010). Among children, the presence of PLEs is more common, with a median of 17% among children aged 9-12 years, although these rates appear to decline with age (Kelleher *et al.*, 2012a). Evidence from birth cohorts and general population samples assessing PLEs by questionnaires or by clinical interview have found that the presence of PLEs is associated with increased risk for later development of psychosis (Dominguez *et al.*, 2011, Fisher *et al.*, in press, Poulton *et al.*, 2000, Welham *et al.*, 2009b, Werbeloff *et al.*, 2012, Zammit *et al.*, in press). During childhood, PLEs are known to aggregate in families, are heritable, and they are associated with other risk factors for psychosis including obstetric complications, cannabis use, trauma, and emotional, cognitive, and behavioural difficulties (Kelleher *et al.*, 2012a, Polanczyk *et al.*, 2010). Self-report questionnaires typically yield higher prevalence rates of PLEs than clinical interviews (Van Os *et al.*, 2009). However, a recent study found that brief community screening questionnaires subsequently verified by follow-up clinical interviews provided good sensitivity and specificity in identifying PLEs among children/adolescents, with one question on auditory hallucinations yielding the highest predictive power (Kelleher *et al.*, 2011). Thus, brief self-reports on questionnaires may provide a valid measure of PLEs in community samples of children.

Screening community samples of children/adolescents for PLEs offers an exciting opportunity for identifying individuals at-risk for schizophrenia or SSD. Samples are larger, non-help seeking, and younger than those identified by UHR criteria, thereby providing an opportunity to study the aetiology of psychosis (Kelleher and Cannon, 2011, Polanczyk *et al.*, 2010).

Cross-sectional data from general population samples indicate significant comorbidity of PLEs with emotional and behavioural problems (Barragan *et al.*, 2011, Kelleher *et al.*, 2012b). Although rates of PLEs appear to decline through childhood and adolescence (Kelleher *et al.*, 2012a), associations between psychopathology and PLEs appear to strengthen with increasing age (Bartels-Velthuis *et al.*, 2010, Kelleher *et al.*, 2012b), particularly among youth experiencing persistent PLEs (Mackie *et al.*, 2011, Rössler *et al.*, 2007, Thapar *et al.*, 2012, Wigman *et al.*, 2011). Therefore, it may not be only the presence of PLEs per se, but also the associated psychopathology which confers vulnerability for psychosis (Kaymaz and Van Os, 2010). However, whilst PLEs may predict later psychoses, the prevalence of PLEs in the general population exceeds that of psychotic disorders, and recent evidence indicates that PLEs, in isolation, are a relatively non-specific marker of risk for later mental disorders (Fisher *et al.*, in press, Poulton *et al.*, 2000, Werbeloff *et al.*, 2012). The annual risk of transitioning to psychosis has been found to be 0.6% for individuals reporting PLEs (Kaymaz *et al.*, 2012) and 22% of help-seeking individuals meeting UHR criteria (Fusar-Poli *et al.*, 2012a).

Recent studies have assessed prodromal symptoms among children/adolescents presenting with PLEs. Among a sample of 58 individuals aged between 16 and 40 years drawn from the general population, only 1% met UHR criteria based on the presence of Attenuated Psychotic Symptoms (Schimmelmann *et al.*, 2013). A further study of 212 adolescents aged 11 to 13 years who reported experiencing PLEs at clinical interview found that 8% met UHR criteria (Kelleher *et al.*, 2012d). This latter study found that more adolescents met criteria for Brief Limited Intermediate Psychotic Symptoms than Attenuated Positive Symptoms, suggesting that, among non-help seeking adolescents experiencing PLEs, the presence of Brief Limited Psychotic Symptoms warrants further investigation.

1.7 A triad of putative antecedents of schizophrenia

A more effective strategy for identifying children who will subsequently develop schizophrenia or SSD may be to use a combination of antecedents of schizophrenia. Laurens and colleagues developed a novel, inexpensive and feasible method for screening community samples of children aged 9-12 years, using child- and caregiver-questionnaires, to identify children who experience a triad of antecedents of schizophrenia (ASz), including: (i) caregiver-reported speech and/or motor development lags or problems; (ii) child-reported internalising problems, and/or caregiver-reported externalising and/or peer-relationship problems in the clinical range (i.e., scoring in approximately the top tenth percentile of UK population norms); and (iii) child-reported PLEs (Laurens *et al.*, 2007). Prospective longitudinal studies of population cohorts and offspring of parents with schizophrenia have shown that these factors distinguish children who later develop schizophrenia from those who do not. In this novel approach, typically developing children (TD) were identified as having none of the antecedents nor a positive family history of schizophrenia or SSD. A more detailed examination of recruitment and feasibility of this novel early identification strategy and the characteristics of ASz and TD children are provided in Chapters Two and Three.

1.8 Summary

Prospective longitudinal studies of population cohorts and of offspring of parents with schizophrenia, retrospective studies of childhood characteristics of adults with schizophrenia concur in showing that children who later develop schizophrenia are characterised by abnormalities in motor and language function, cognitive abnormalities, disturbances in social, emotional and behavioural functioning, PLEs, and neuroanatomical abnormalities. A positive family history of schizophrenia identifies only a subset of children who subsequently develop the illness. Symptomatic, help-seeking individuals at imminent risk for psychosis have been identified based on the

presence of attenuated psychotic symptoms, positive family history of schizophrenia, or self-report “basic symptoms”, but these studies provide little information on the childhood antecedents of the disorder. In community samples, children and adolescents reporting PLEs show increased risk of subsequent schizophrenia and other mental disorders. Thus, a more effective strategy to identify children at elevated risk for schizophrenia may be to use a combination of antecedents of schizophrenia that have been replicated in different studies.

Chapter 2 Child Health and Development Study: Background, rationale and evidence

Overview of chapter aim

This chapter outlines the rationale and background of the Child Health and Development Study (CHADS) study. Finally, a brief review of existing evidence indicating that ASz children present with dysfunctions characteristic of individuals with schizophrenia is provided.

2.1 Background and rationale

Vulnerability to schizophrenia most likely reflects a complex interplay of genetic and environmental factors which influence brain development (Tandon *et al.*, 2008a). The neurodevelopmental hypothesis of schizophrenia posits that social, emotional, behavioural, and cognitive abnormalities are apparent prior to the onset of overt clinical symptoms (for reviews: Matheson *et al.*, 2011, Niemi *et al.*, 2003, Rapoport *et al.*, 2005, Schenkel and Silverstein, 2004, Tarbox and Pogue-Geile, 2008, Welham *et al.*, 2009a). A multifactorial, polygenic model of schizophrenia assumes that multiple vulnerability factors of small to moderate effects contribute to an individual's overall risk of developing psychosis (Erlenmeyer-Kimling, 2000).

Evidence from prospective population cohort studies, "follow-back" studies of individuals with schizophrenia, and investigations of young relatives at elevated risk for the development of schizophrenia by virtue of having a family member with the disorder indicates that biological, psychological and social factors are associated with the development of schizophrenia or SSD. However, as the level of risk associated with each individual risk factor for the disorder may be small, investigators on the CHADS study incorporated the most replicated, predictive, and sensitive of antecedents into a

questionnaire designed to identify children aged 9 to 12 years presenting of a triad of antecedents of schizophrenia or SSD (Laurens *et al.*, 2007). It was reasoned that multiple developmental risk factors may provide a powerful method for detecting risk to schizophrenia during childhood. Indeed, previous studies indicate a multiplicity of potential risk factors for schizophrenia (Keshavan *et al.*, 2005), yet there are few prospective studies examining the predictive effect of multiple individual and biological factors.

As shown in Table 3, prospective longitudinal cohort studies and a prospective investigation of offspring born to a parent with schizophrenia indicate that individuals who develop schizophrenia in adulthood exhibit significant delays in reaching early developmental motor milestones (e.g., learning to sit, stand or walk unaided), and display childhood motor development and speech difficulties compared to individuals without schizophrenia (Bearden *et al.*, 2000, Cannon *et al.*, 2002, Fish *et al.*, 1992, Isohanni *et al.*, 2001, Isohanni *et al.*, 2004, Jones *et al.*, 1994, Rosso *et al.*, 2000).

Based on self-report, parent, and teacher report, prospective studies of population cohorts and studies of young offspring with a parent with schizophrenia consistently demonstrate that between early childhood and mid-adolescence (4 to 15 years) individuals who develop schizophrenia in adulthood are characterised by social withdrawal, peer difficulties, anxiety, depression, and conduct and attention deficit hyperactivity disorders relative to those without a diagnosis of schizophrenia or SSD in adulthood (Amminger *et al.*, 1999, Bearden *et al.*, 2000, Cannon *et al.*, 2002, Cannon *et al.*, 2001, Crow *et al.*, 1995, Done *et al.*, 1994, Jones *et al.*, 1994, Kim-Cohen *et al.*, 2003, Marcus *et al.*, 1987, Olin and Mednick, 1996, Roff and Fultz, 2003, Welham *et al.*, 2009b). In addition, prospective cohort studies provide evidence that the presence of PLEs in childhood and adolescence is strongly associated with schizophrenia or SSD in

adulthood (Fisher *et al.*, in press, Poulton *et al.*, 2000, Welham *et al.*, 2009b, Zammit *et al.*, in press).

Based on the evidence presented in Table 3 (updated to reflect further published research than presented in Laurens *et al.*, 2007) ASz children were defined as having: (1) a caregiver-report of a motor and/or speech delay and/or abnormality; (2) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (SDQ: Goodman, 2001); and (3) a child-reported "certainly-true" response on at least one of nine PLE items assessing hallucination- and delusion-like experiences (Laurens *et al.*, 2012).

Given a lifetime risk of schizophrenia of approximately 0.7% in the general population (Saha *et al.*, 2005), investigators envisaged that large numbers of children could only be screened for childhood antecedents using a questionnaire (Laurens *et al.*, 2011). It was anticipated that this approach might capture a broader range of children vulnerable for the disorder than could be offered by identifying only children/adolescents with a positive family history of schizophrenia, and a smaller number with higher risk than studies using only one antecedent such as PLEs to select children at-risk for the disorder.

An initial pilot study based on 264 child and caregiver questionnaires reported that 9.2% of boys and 4.1% of girls were characterised by the ASz triad although greater numbers were reported by each component of the triad (Laurens *et al.*, 2007). The findings of this pilot investigation indicated that having school children and their caregivers complete the brief questionnaires was a feasible and relatively inexpensive method to identify children who may be at elevated risk for schizophrenia or SSD.

Subsequently, among 1,347 children and caregivers with available data it was found that 9.5% of children met ASz criteria and 23.6% reported no antecedent (Laurens *et al.*, 2011). More specifically, approximately one-third of children experienced SDQ psychopathology scores in the clinical range, with caregivers reporting peer relationship difficulties for 13.9%, conduct problems for 10.8%, hyperactivity-inattention problems for 9.6% of the sample, and 12.6% of children reporting emotional symptoms. In total, 26.4% of caregivers reported a speech and/or motor problem with speech delays/abnormalities being more common (21.5%) than motor delays/problems (9.4%).

The prevalence rate of ASz was significantly greater among children of African-Caribbean descent relative to children of white British heritage, but was not associated with migrant status (Laurens *et al.*, 2008). Recent work on the larger community sample of ASz children extended these findings and reported that the ASz prevalence rate was elevated in children of black African ethnicity (Laurens *et al.*, 2011). These findings are consistent with the increased prevalence of schizophrenia and psychotic symptoms among individuals of African-Caribbean origin living in the United Kingdom (Fearon *et al.*, 2006, Johns *et al.*, 2004, Johns *et al.*, 2002, King *et al.*, 2005) and provide further evidence that ASz criteria may be a more sensitive and specific marker of the development of schizophrenia than PLEs alone.

Consistent with the earlier study (Laurens *et al.*, 2007), 63% of children reported experiencing at least one ‘certainly true’ PLE(Laurens *et al.*, 2011). The three most commonly reported experiences related to auditory and visual hallucinations and paranoid thoughts. Recent work validating PLE screening questionnaires using clinical interviews found that these three types of PLEs demonstrated good-to-excellent predictive power for psychotic symptoms at interview (Kelleher *et al.*, 2011). Furthermore, over two-thirds (69%) of children presenting with the ASz triad reported

distress and/or functional impairment associated with PLEs. Individual reactions to and coping with PLEs may be important in determining outcomes (Garety and Freeman, 1999, Krabbendam *et al.,* 2002) Moreover, distress associated with PLEs may cause persistence over time which could play a role in the later transition to psychosis (Van Os *et al.*, 2009). Overall, these findings indicate the comorbidity of PLEs with psychopathology among children in the community.

Cross-sectional data from the general population indicate significant comorbidity of PLEs with emotional and behavioural problems (Barragan *et al.*, 2011, Kelleher *et al.*, 2012b). The persistence of these experiences is also associated with increased psychopathology and social impairments (Cougnard *et al.*, 2007, Dominguez *et al.*, 2011, Woods *et al.*, 2009) More recently, investigators on the CHADS study sought to explore whether PLE persistence was associated with later internalising and externalising psychopathology (Downs *et al.*, 2013). A large sample of 8,099 children aged between 9 and 12 years completed the screening questionnaire to assess antecedents of schizophrenia. A subsample of 547 children again completed the questionnaire approximately two years later. Results indicated comparable PLE prevalence rates (30%) and PLE persistence rates (39%) to those reported in adolescent cohorts using self-report PLE questionnaires (De Loore *et al.*, 2011, Dominguez *et al.*, 2011, Escher *et al.*, 2002, Kelleher *et al.*, 2011, Yung *et al.*, 2009). In addition, those children with persisting PLEs displayed more internalising and externalising psychopathology at follow-up compared to those children with no PLEs and those with a remitting PLE trajectory. These findings contribute to the growing body of evidence which demonstrates that persistence of PLEs during childhood and adolescence may be important in identifying children at elevated risk of later psychopathology (Bartels-Velthuis *et al.*, 2011, De Loore *et al.*, 2011, Wigman *et al.*, 2011).

Table 3. Review of the antecedents of schizophrenia

Reference	Sample	Age	Association between antecedent and outcome
Speech and motor abnormalities			
Fish *et al.*, (1992)	New York prospective longitudinal high-risk infant study	During first 2 years	Future cases diagnosed with a schizophrenia spectrum disorder in adulthood had greater delays in motor development.
Jones *et al.*, (1994)	British 1946 Birth Cohort	2 and 6 years	Non-structural speech problems in 11.1% of children who later developed schizophrenia. 5.1% in comparison group. 7.4% of future schizophrenia cases had not learnt to sit, stand, or walk unaided. 1.6% in comparison group.
Bearden *et al.*, (2000)	National Collaborative Perinatal Project (NCPP)	7 years	Abnormal speech predicted future schizophrenia (OR:12.7).
Rosso *et al., (*2000)	NCPP	4 and 7 years	Unusual movements increased risk of later schizophrenia.
Isohanni *et al.*, (2001; 2004)	Northern Finland 1966 Birth Cohort	N/A	Future schizophrenia associated with later age for reaching developmental milestones (standing and walking unaided)
Cannon *et al.*, (2002)	Dunedin Multidisciplinary Health and Development Study	3, 5, 7, and 9 years	Poor receptive language skills and motor development (except at 7 years) relative to controls at all ages.
Social, emotion and behavioural problems			
Marcus *et al.*, (1987)	Israeli High-Risk Study	8-14 years	Future schizophrenia cases all presented with neurobehavioral deficits characteristic of attention deficit disorder. 8 out of 9 future cases reported poor interpersonal behaviour: males were reported to be more anti-social and/or withdrawn; and females more socially withdrawn.

Reference	Sample	Age	Association between antecedent and outcome
Jones *et al.,* (1994)	British 1946 Birth Cohort	4, 6,13, and 15 years	Solitary play predicted later schizophrenia Social anxiety linearly associated with schizophrenia Schizophrenia cases significantly more anxious (OR:1.3)
Done *et al.,* 1994	British 1958 Birth Cohort	7 and 11 years	Schizophrenia cases more socially maladjusted. Male future schizophrenia cases displayed more externalising behaviours (7 and 11 years). Female future schizophrenia cases more socially withdrawn.
Crow *et al.,* (1995)	National Child Development Study (NCDS)	7 and 11 years	Schizophrenia cases compared to non-diagnosis cases more anxious and hostile. Female schizophrenia cases: withdrawn and depressed. Males: more depressed.
Olin and Mednick (1996)	Copenhagen High-Risk Project	15 years	Male future schizophrenia cases more socially withdrawn and emotional. Female future cases more anxious.
Amminger *et al.,* (1999)	New York High-Risk Project	Mean age 9 years	Individuals who developed schizophrenia-related psychoses significantly more likely to have behavioural problems.
Bearden *et al.,* (2000)	NCPP	7-8 years	Social maladjustment significantly increased the odds of schizophrenia (OR:2.5).
Cannon *et al.,* (2001)	Follow-back study of attendees at a child psychiatric department	13-14 years	Significant peer difficulties and abnormal suspiciousness or sensitivity associated with later development of schizophrenia
Cannon *et al.,* (2002)	Dunedin Multidisciplinary Health and Development Study	5, 7, 9, and 11 years	Significantly higher ratings of internalising problems among schizophreniform cases relative to controls.
Kim-Cohen *et al.,* (2003)	Dunedin Multidisciplinary Health and Development Study	11 and 15 years	Among schizophreniform cases significantly higher prevalence of juvenile anxiety disorder (38%), depression (32%), attention deficit disorder (20%), and conduct disorder/oppositional defiant disorder (40%) compared to no-diagnosis controls.

Reference	Sample	Age	Association between antecedent and outcome
Roff and Fultz, 2003	Follow-back study of attendees at a child psychiatric department	8 years	Future schizophrenia cases characterised by peer difficulties and at 9 years were more socially withdrawn.
Welham *et al.*, (2008)	Mater-University Study of Pregnancy and Outcomes	5 and 14 years	Screen-positive non-affective males reported higher levels of aggression at 5 and 14 years based on psychopathology measure (OR:6.8).
Psychotic like-experiences			
Poulton *et al.*, (2000)	Dunedin Multidisciplinary Health and Development Study	11 years	Children reporting PLEs at clinical interview were 16 times more likely to have a schizophreniform diagnosis at 26 years relative to those children who did not.
Welham *et al.*, (2008)	Mater-University Study of Pregnancy and Outcomes	14 years	Screen-positive non-affective cases reported significantly more PLEs at 14 years based on psychopathology measure.
Zammit *et al.*, (2013)	Avon Longitudinal Study of Parents and Children (ALSPAC)	12 years	Odds of having a psychotic disorder at 18 years were higher in those with suspected PLEs at 12 years (OR: 5.6) and definite PLEs at 12 years (OR:12.7)
Fisher *et al.*, 2013	Dunedin Multidisciplinary Health and Development Study	11 years	At 11 years, children reporting strong PLEs at clinical interview were at significantly elevated risk (RR=7.24) of developing schizophrenia at 38 years compared to individuals without schizophrenia.

OR=Odds ratio; RR=Relative risk

2.2 Evidence from the CHADS study

Only longitudinal follow-up of ASz and typically developing (TD) children will establish the degree to which the antecedent triad predicts later schizophrenia or other psychiatric disorders. However, published work has shown that ASz children, compared with TD children are characterised by features observed among adults with schizophrenia.

2.2.1 Neurocognitive function

An examination of neurocognitive performance among 28 ASz and 28 TD children matched on sex and parents' socio-economic status (SES) observed significant group differences on four out of seven domains of cognitive functioning. ASz children were characterised by a moderate overall mean effect size impairment (d=0.52) relative to TD peers (Cullen *et al.*, 2010). Specifically, ASz children were impaired on measures of general intelligence, verbal memory, working memory, and Executive Function (EF)-inhibition. These cognitive domains have been reported to be impaired among adults with schizophrenia, individuals experiencing FEP, prodromal youth and young relatives of individuals with schizophrenia (for reviews: Addington and Barbato, 2012, Agnew-Blais and Seidman, 2013, Dickinson *et al.*, 2007, Fioravanti *et al.*, 2005, Forbes *et al.*, 2006, Fusar-Poli *et al.*, 2012b, Mesholam-Gately *et al.*, 2009, Reichenberg and Harvey, 2007).

2.2.2 Event-related processing (ERP)

An investigation of brain function abnormalities during event-related processing (ERP) tasks among 22 ASz and 26 TD children reported reduced ERN amplitude of error-related negativity event-related potential component generated in the anterior cingulate that indexes internal monitoring of behaviour (Laurens *et al.*, 2010). ASz children aged 9-12 years presented early error-processing deficits that have also been

observed among adults with schizophrenia (Alain *et al.*, 2002, Bates *et al.*, 2004, Mathalon *et al.*, 2002, Morris *et al.*, 2006).

2.2.3 Movement abnormalities

Twenty-one ASz children relative to 31 TD peers displayed significantly more dyskinetic movement abnormalities in facial and upper body regions (Macmanus *et al.*, 2012). Dopamine dysfunction in the striatum has been reported in a recent study of prodromal individuals and may be associated with psychotic symptoms (Howes *et al.*, 2009). The presence of PLEs and dyskinesias among ASz children tentatively suggest that striatal dopamine irregularities may be present well before illness onset.

2.2.4 Temporal lobe abnormalities

Structural brain abnormalities of the temporal lobes have been reported among 20 ASz compared to 20 TD children. These abnormalities of grey and white matter volume in the temporal lobes are consistent with regions affected among individuals experiencing FEP and those presenting prodromal symptoms (Cullen *et al.*, 2013).

2.2.5 Social withdrawal

ASz children aged 9 to 14 years displayed a large effect size impairment in social withdrawal compared to TD peers, a significant but weaker effect was also reported among children with a positive family history of schizophrenia or SSD (Matheson *et al.*, 2013). In addition, meta-analyses indicated that social withdrawal in childhood and adolescence characterises individuals who develop schizophrenia in adulthood compared to those who do.

2.2.6 Stress

A recent study examined negative life events and daily stressors among ASz and FHx children relative to TD children. The results indicate that both ASZ and FHx children report more environmental stressors and greater distress resulting from these

events compared to TD peers (Cullen *et al.*, submitted). ASz children experienced a greater number of and sensitivity to daily stressors, while FHx children reported a greater number of negative life events and were distressed by these experiences. While psychological stress has been implicated in the development of schizophrenia, it has yet to be fully characterised amongst children who are at-risk for the disorder.

2.3 Summary

A novel strategy using a combination of antecedents of the disorder to identify at-risk children may maximise opportunities to prospectively examine the development of schizophrenia and SSD. Evidence provided in this chapter indicates that questionnaires completed by school children and their caregivers identified children putatively at-risk for schizophrenia. Findings from laboratory studies suggest that ASz children, compared to TD children are characterised by features qualitatively similar to those observed among adults with schizophrenia. Research indicates that impaired cognitive and emotion processing abnormalities in childhood may index vulnerability to schizophrenia. Thus, there is a need to further establish the validity of ASz criteria as an early at-risk strategy.

Chapter 3 Selection of participants from the CHADS

Aims of chapter

This chapter outlines the methodology of CHADS and compares the children from CHADS who participated and who did not participate in the studies reported in this thesis.

3.1 Sample and recruitment

The CHADS is a prospective longitudinal study investigating cognitive, biological and psychosocial measures among children deemed to be at-risk for schizophrenia or SSD. Ethical review of the study was provided by the Joint South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry Research Ethics Committee. 106 children were recruited using two different strategies described below.

3.1.1 Recruitment of ASz and TD children

Children aged 9-12 years and their primary caregiver completed questionnaires that assessed the presence of well-known antecedents of schizophrenia. Children were recruited from 69 Greater London primary schools within the boroughs of Southwark, Lambeth, Lewisham, Tower Hamlets, Brent, Bromley, Croydon and Harrow using an "opt out" procedure. After approval of the study by the heads of each school, children took home letters to caregivers that described the research project and noted that their child, along with all his/her classmates, would be completing a questionnaire focused on emotional and behavioural difficulties, on a specific day. If caregivers did not wish their child to complete the questionnaire, they were required to return a form to the school prior to the day of testing. Approximately 90% of children were recruited from the schools in the first five boroughs, which rank among the most deprived 15% of all English local authorities (Laurens *et al.*, 2011).

Researchers read aloud questionnaires to classes of school children in order that they completed questionnaires independently (see appendix III for child version of questionnaire). When completed, each child was given an envelope for their primary caregivers that contained a caregiver version of the questionnaire, a request to agree to participate in subsequent phases of the study, and a reply-paid envelope (see appendix IV for caregiver version of screening questionnaire). In total, 1,343 children and caregivers completed screening questionnaires. Among these, 9.4% of children met ASz criteria, and 22.5% of children did not present with any of the antecedents of schizophrenia and were defined as typically developing (TD). Over half of these families (55.4%) indicated a willingness to be contacted for further research. Of the 64 ASz and 86 TD children invited to participate in the baseline assessment phase of the study that included neurocognitive assessments, 38 (59%) ASz and 50 (58%) TD children and caregivers agreed. Eleven of these potential participants were subsequently excluded from CHADS due to insufficient English ability to complete assessments, neurological disorder, and diagnosis of autism or Asperger's disorder. The final sample consisted of 32 ASz and 45 TD children who had completed baseline cognitive assessments.

ASz criteria was defined as: (1) a child-reported "certainly-true" response on at least one of nine psychotic like-experiences (PLE) items assessing hallucination- and delusion-like experiences (Laurens *et al.*, 2012); (2) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (Goodman, 2001); and (3) a caregiver-report of a motor and/or speech delay and/or abnormality (Laurens *et al.*, 2007). TD children were primary school children who presented none of the three ASz criteria on screening questionnaires and

who also had no first-, second-, or third-degree relative with a schizophrenia spectrum disorder later reported by the caregiver at the Family Interview for Genetic Studies (FIGS: Maxwell, 1992).

3.1.2 Recruitment of children with a family history of schizophrenia

In order to identify children with a family history of schizophrenia or schizoaffective disorder (FHx), the screening questionnaire included items on mental disorders among relatives. Approximately 3.4% of the 1,204 caregivers indicated a positive family history of a schizophrenia spectrum disorder for their child. Additionally, children aged 9-12 years were recruited as relatives of patients receiving treatment within the South London and Maudsley National Health Service Foundation Trust. Over one-third of FHx families (37%) recruited either through schools or as relatives of patients, declined to participate after initial contact. More than one-half of the 29 participating FHx children were recruited from the school screening procedure (59%) and the remainder through contacts with patients. Children with a family history of schizophrenia (FHx) comprised children with a first-degree relative (parent) with schizophrenia (n=9) or schizoaffective disorder (n=2), two second-degree relatives (n=2) with schizophrenia (uncles and aunt/grandmother), and one second-degree relative (uncle, aunt, or grandparent) with schizophrenia (n=16) confirmed by FIGS interview with the child's primary caregiver (Maxwell, 1992). Five FHx children also met full ASz criteria.

3.1.3 Participants in the initial laboratory assessments

The final sample of children who completed the initial laboratory assessments consisted of 27 FHx (2 additional children were recruited at a subsequent follow-up assessment phase), 32 ASz and 45 TD children (a flow diagram of the recruitment process from school screening to follow-up assessments is included in Appendix V). Children recruited into the study had never experienced a psychotic episode or taken

anti-psychotic medication, and none presented with a neurological disorder, learning difficulties (IQ < 70), or a diagnosis of autism or Asperger's disorder. In the studies reported in this thesis, sample sizes differ slightly and the reasons are described in the report of the study.

3.1.4 Participants in the follow-up laboratory assessments

When children were aged 11 to 14 years, approximately two years after initial assessments, families were invited to again participate and children completed assessments of cognitive, biological, and psychosocial functioning (FU24). Again, approximately two years later, this invitation was repeated when children were aged between 13-16 years (FU48). Table 4 provides sample sizes for ASz, FHx, and TD groups at each of the three assessments.

Table 4. Sample sizes for ASz, FHx, and TD children at each assessment phase

	FHx[a]	ASz	TD
Baseline assessments	27	32	45
FU24 assessments	26[b]	30[c]	43[d]
FU48 assessments	20[e]	19[f]	36[g]

Notes: [a] two additional cases recruited at FU24; [b] 3 declined to participate or non-contactable; [c] 2 declined to participate or non-contactable; [d] 1 dropped from study after baseline assessments and 1 declined to participate or non-contactable; [e] 5 declined to participate or non-contactable and 4 assessments outstanding; [f] 8 declined to participate or non-contactable and 5 assessments outstanding; and [g] 1 dropped from study after baseline assessments, 3 declined or non-contactable and 5 assessments outstanding.

At follow-up assessments, the following criteria was used to identify continued assignment to the ASz group: scores in the "borderline" range on the psychopathology subscales of SDQ [~top 20% of UK population norms; (Goodman, 2001)], and (2) a child report endorsing the presence of a PLE as at least "somewhat true" similar to the criterion used by Kelleher *et al.*, 2011. Details of ASz participants excluded from

specific studies because they no longer met ASz criteria are noted in the report of each study (Chapters Seven and Nine).

3.2 Procedure

Eligible children completed a battery of neurocognitive assessments in addition to biological and psychosocial measures, at each of the three assessments phases spaced at approximately two year intervals providing longitudinal data spanning from 9-16 years. Assessments lasted approximately eight hours and took place over a period of two days. At each assessment children provided written assent, and caregivers provided written informed consent, for participation in the study.

3.3 Measures

Only measures used to identify participants and details of cognitive and facial emotion processing measures reported in this thesis are described.

3.3.1 Identifying antecedents of schizophrenia

Questionnaires completed by children comprised of two measures (see appendix III).

Strengths and Difficulties Questionnaire (SDQ: Goodman, 2001): The SDQ is a well-validated instrument for assessing social, emotional, and behavioural problems in community samples, with demonstrated criterion validity as a screening device for detecting mental health disorders (Goodman, 2001). The SDQ comprises 25 items assessing five domains of psychopathology (Emotional Symptoms, Conduct Problems, Hyperactivity-Inattention, Peer Relationship Problems, and Prosocial Behaviour (personal strengths). Screening measures included Prosocial Behavioural items but were not included in the antecedent triad construction (Laurens *et al.*, 2007). The four subscales each contained five items, with each item rated on a three-choice response scale: ‘0=not true’, ‘1=somewhat true’ or ‘2=certainly-true’. Normative bandings of

"Normal", "Borderline", and "Abnormal" for each subscale have been established (Goodman *et al.*, 2003). Internal reliability, test-retest stability, and validity of the child- and caregiver-report SDQ is well established (Goodman, 2001, Goodman *et al.*, 2003), including for child-report by children as young as eight years (Riso *et al.*, 2010). The SDQ was re-administered at FU24 and FU48.

Psychotic like-experiences (PLEs: Laurens et al., 2012, Laurens et al., 2007): Nine self-report PLE items assessed hallucination-like and delusion-like experiences, with high internal consistency (α= 0.82) (Laurens *et al.*, 2007). Five questions were adapted from the Diagnostic Interview Schedule for Children (DISC: Costello *et al.*, 1982), and four additional items were added to assess a broader range of PLEs (Laurens *et al.*, 2007). A list of PLE items are provided in tables 7 and 8 below. Each PLE item was rated on a three-choice response scale: '0=not true', '1=somewhat true' or '2=certainly-true'. The nine items load strongly on a single latent construct that is distinct from internalising and externalising symptom dimensions (Laurens *et al.*, 2012). Good criterion validity has been indicated between seven similar questionnaire PLE items self-reported by children aged 11-13 years and clinician-rated psychotic symptoms reported at interview (Kelleher *et al.*, 2011). PLEs were assessed again during FU24 and FU48 month research assessments.

A third questionnaire was completed by caregivers (see appendix IV).

Speech/motor development delays/abnormalities (Laurens et al., 2007): In the absence of an established measure for obtaining retrospective reports by caregivers of milestone attainment in walking and speaking, ratings of developmental delays/abnormalities were obtained using three quantitative items (comprising a selection of five age-bands to index marked deviations in age of milestone attainment [>95% percentile of World Health Organisation [1986] population norms]) and six

qualitative items (indexing reports of medical/allied health professional concerns regarding development or significant parental concerns for which professional help was sought). This questionnaire was completed by caregivers during baseline assessments only.

3.3.2 Characteristics of families

Family Interview for Genetic Studies (FIGS: Maxwell, 1992): Caregivers completed the Family Interview for Genetic Study, a semi-structured interview administered by trained researchers used to ascertain family history of mental disorders. Caregivers also provided information on ethnicity of relatives.

National Statistics Socio-Economic Classification Method (N-SEC; Rose and Pevalin, 2003): Interviews with caregivers elicited information to derive eight-socio economic classes based on parents' occupation. In families where two parents were employed, a single class based on the caregiver with the highest occupational status was used.

3.3.3 Measures of cognitive functioning

A brief description of each neurocognitive measure and manual derived population means and standard deviation (SD) of standardised scores comprising the test battery is provided in Table 5.

General Intelligence (IQ). IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999), which includes four subtests: vocabulary, block design, similarities, and matrix reasoning. IQ estimates in Chapter Five were derived for verbal IQ (vocabulary and similarities), performance IQ (block design and matrix reasoning), and full-scale IQ (sum of standardised scores for all four subtests). IQ estimates in Chapter Seven were derived from vocabulary and matrix reasoning subtests to form a 2-subtest IQ score.

Scholastic Achievement. Scholastic achievement was assessed using the Wechsler Individual Achievement Test - Second UK Edition (WIAT-II-UK: Wechsler, 2005), which measures academic skills for children aged 4 to 16 years and is reflective of the UK national curriculum. The thesis employed three subtests: word reading, numerical operations, and spelling. In Chapter Five, a scholastic achievement domain score was created by adding standardised scores for each participant on word reading, numerical operations, and spelling subtests and then dividing the total score by number of subtests.

Memory. Memory was assessed using the verbal memory (story memory and verbal learning), visual memory (design memory and picture memory), verbal working memory subtests of the Wide Range Assessment of Learning and Memory (WRAML2:Sheslow and Adams, 2003).

Executive Function. Executive functioning (EF) was measured using the verbal fluency (letter fluency, category fluency, and category accuracy scores), colour word interference test (inhibition and inhibition/switching scores), and towers test (achievement score) subtests of the Delis-Kaplan Executive Function System (DKEFS: Delis *et al.*, 2001).

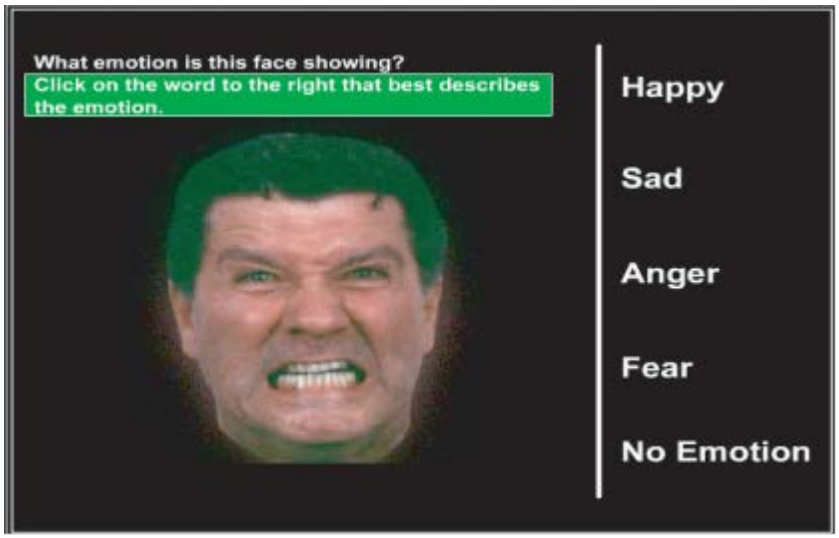
Table 5. Description of neurocognitive tests

Cognitive measure	Test Description	Mean (SD)
Intelligence		
Verbal Comprehension		
- Vocabulary	Define orally and visually presented words	50 (10)
- Similarities	Identify similarities between pairs of words	50 (10)
Perceptual Reasoning		
- Block Design	Replicate geometric patterns using two-coloured cubes within a specified time limit	50 (10)
- Matrix Reasoning	Choose one shape from five to complete a pattern	50 (10)
Scholastic Achievement		
- Word Reading	Read aloud a word list	100 (15)
- Numerical Operations	Complete mathematical problems	100 (15)
- Spelling	Write verbally presented words	100 (15)
Memory		
Verbal Memory		
- Story Memory	Immediate recall of details from two short stories read aloud	10 (3)
- Verbal Learning	Immediate free recall of word list (four trials)	10 (3)
Visual Memory		
- Design Memory	Immediate recall of five geometric designs	10 (3)
- Picture Memory	Identify differences between four similar pairs of pictures.	10 (3)
- Verbal Working Memory	Immediate recall of word lists by animal and non-animal categories	10 (3)
Executive Functioning		
Verbal Fluency		
- Letter Fluency	Generate words beginning with F, A, and S in 60 seconds	10 (3)
- Category Fluency	Generate animals and boys' names in 60 seconds	10 (3)
- Category Accuracy	Alternatively generate words from fruits and furniture categories in 60	10 (3)
Colour Word interference		
- Inhibition	Name ink colour of colour words printed in different colour ink	10 (3)
- Inhibition/Switching	As for Inhibition subtest; or, reading colour word (ignore printed ink	10 (3)
Towers Test		
- Towers Test Achievement score	Build towers using one to five pegs in the fewest possible number of moves	10 (3)

3.3.4 Facial emotion processing

Facial emotion recognition (FER) was assessed using the Penn Emotion Recognition Task (ER40), a computerised task that requires participants to correctly recognise facial emotions. The ER40 comprises 40 colour photographs of faces displaying happy, sad, angry, fearful, and neutral facial expressions (8 photographs of each emotional expression). The photographs were balanced for the intensity of emotion expressed (mild or high), and the age, gender, and ethnicity of the faces. Each face was presented serially on a computer screen, in random order, with five response options displayed to the right of each photograph (i.e., “happy”, “sad”, “angry”, “fear”, or “no emotion” [neutral]). For each photograph, participants were instructed to select the response that best described the displayed emotion, as quickly and as accurately as possible (see Figure 1). Responses were selected by computer-mouse click. Each face was displayed until a response was recorded. Details of task construction and ratings have been reported previously (Gur *et al.*, 2002).

Figure 1. Example of a high intensity angry face on the ER40 task



3.4 Comparisons of ASz and TD children who did and who did not participate in the studies reported in the thesis

Chi-square analyses were conducted to examine group differences in sex and ethnicity between ASz and TD children who completed screening questionnaires and contributed data to the studies for this thesis compared to ASz and TD who completed screening questions but did not supply contact information for further research (ASz-no, TD-no) and did not participate. Logistical regression analyses on each of the antecedents of schizophrenia were conducted to establish whether the presence /absence of each antecedent component were similar among ASz children who contributed data to the studies in this thesis as compared to ASz-no children who completed screening questionnaires but did not contribute data to the study chapters of this thesis.

TD children were defined as having none of the antecedents of schizophrenia but could report 'borderline' SDQ problems or 'somewhat true' PLEs. Therefore, logistical regression analyses based on the presence/absence of 'borderline' SDQ scores and 'somewhat true' PLEs were conducted to examine differences between TD and TD-no children. A previous investigation observed differences between boys and girls on specific ASz components and overall prevalence of ASz triad (Laurens *et al.,* 2011). Therefore, sex was included as a covariate in all regression analyses. FHx group were not included in this analyses as recruited on the basis of a positive family history alone.

Table 6 presents comparisons of sex and ethnicity of ASz and TD children who did and who did not participate in studies reported in the thesis. ASz and ASz-no children did not differ as to the proportions that were male, but did differ as to ethnicity. No significant differences between TD and TD-no children were found for sex and ethnicity.

Table 6. Comparisons of sex and ethnicity among ASz, ASz-no, TD, and TD-no children

	ASz (n=32)		ASz-no (n=98)		TD (n=45)		TD-no[b] (n=255)		Statistics
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Sex (Male)	22	(69)	64	(65)	19	(43)	97	(38)	**ASz Vs ASz-no**: X^2=0.13, (df=1), p=0.72 **TD Vs TD-no**: X^2=0.42, (df=1), p=0.52
Ethnicity[a]									
White British	7	(22)	25	(26)	23	(52)	114	(45)	**ASz Vs ASz-no**: *Fishers Exact Test*= p=<0.01 **TD Vs TD-no**: X^2=7.2, (df=3), p=0.06
White Other	8	(25)	3	(3)	9	(21)	25	(10)	
Black African and African-Caribbean	9	(28)	58	(59)	7	(16)	75	(29)	
Other	8	(25)	12	(12)	5	(11)	41	(16)	

Notes: ASz = ASz children who participated; ASz-no = ASz children completed screening questionnaires but did not participate in the laboratory assessments; TD = TD children who participated; and TD-no = TD children who completed screening questionnaires but did not participate in laboratory assessments. [a]"Black African and Black African-Caribbean" included children of mixed white-Black African/African-Caribbean ethnicity. "Other" included children predominantly of other mixed ethnicities; and [b] data missing for 4 children.

3.4.1 Comparisons between ASz and ASz-no children

Table 7 presents comparisons of the percentages of ASz and ASz-no children who presented each of the triad components. Results are not corrected to take account of multiple comparisons. Few differences between those who did and did not participate were observed. ASz as compared to ASz-no children reported more emotional problems on the SDQ. Previously, Laurens and colleagues reported that girls meeting ASz criteria were significantly more likely to report emotional difficulties than boys (Laurens *et al.*, 2011). Greater emotional problems among ASz-no children may, in part, reflect sex differences in the prevalence of the ASz triad and the reluctance of girls experiencing emotional problems to participate in further research.

The majority of ASz and ASz-no children reported experiencing more than one "certainly true" PLE, with the most frequently endorsed PLE experienced being auditory hallucinations. The presence of auditory hallucinations as reported on PLE screening questionnaires are known to be a robust predictor of subclinical psychotic symptoms at clinical interview and is consistent with previous findings in the larger CHADS community sample (Laurens *et al.*, 2011). No significant differences between ASz and ASz-no groups were reported on any PLE item, except that ASz-no children were more likely to report unusual perceptual experiences relating to feelings that their body had changed. Table 7 presents percentages of children reporting: (1) distress; (2) impairment; (3) either distress or impairments; and (4) both distress and impairment relating to PLEs. No significant differences between ASz and ASz-no groups were observed for impact or distress.

Table 7. Percentages of ASz (n=32) and ASz-no (n=98) children age 9 to 12 years who present each triad component.

Antecedent	ASz (%)	ASz –no (%)	OR; p
Speech/Motor abnormalities			
Delay or abnormality in speech development	84.4	84.5	1.0; 0.96
Delay or abnormality in motor development or motor coordination problem	32.3	44.9	1.7; 0.22
SDQ psychopathology			
Emotional symptoms (child reported)	21.9	50.0	3.8; 0.01
Conduct problems (care-giver reported)	40.6	31.6	0.7; 0.36
Hyperactivity-inattention (care-giver reported)	40.6	36.1	0.9; 0.72
Peer problems (care-giver reported)	50.1	45.4	0.8; 0.67
Psychotic like-experiences			
More than one 'Certainly true' experience	62.0	75.5	1.8; 0.16
Have you ever heard voices that other people could not hear?	50.0	63.3	1.7; 0.20
Have you ever thought that you were being followed or spied upon?	34.4	54.0	2.3; 0.06
Have you ever seen something or someone that other people could not see?	37.5	33.3	1.9; 0.11
Have you ever known what another person was thinking even though that person wasn't speaking?	34.4	31.6	1.1; 0.76
Have you ever felt as though your body had been changed in some way that you could not understand?	15.6	46.4	4.7; 0.01
Do you have special powers that other people don't have?	37.5	33.3	0.8; 0.67
Have you ever felt that you were under the control of some special power?	18.8	35.7	2.4; 0.08
Have you ever believed that you were being sent special messages through the television?	6.3	17.3	3.1; 0.14
Some people believe that their thoughts can be read. Have other people ever read your thoughts?	9.4	19.4	2.3; 0.74
Do these experiences upset you? [a]	34.8	50.7	2.0; 0.17
Do these difficulties cause you difficulties at home or at school? [a]	39.1	58.9	2.2; 0.10
Experiencing upset OR difficulties due to these experiences [a]	52.2	72.6	2.5; 0.07
Experiencing upset AND difficulties due to these experiences [a]	21.7	37.0	2.2; 0.17

Notes: OR=odds ratio; and [a] Impact of PLEs were based on child reports of "somewhat-true" and "certainly-true" ratings. Impact data on PLEs obtained from a smaller sample (ASz n=23/ASz-no n=75) due to earlier versions of screening questionnaires not containing questions on impact of these experiences.

3.4.2 Comparisons between TD and TD-no children

Table 8 provides percentages of "borderline" SDQ scores and "somewhat true" PLES for TD and TD-no children. Approximately 2% to 14% of TD children and 3% to 7% of TD-no children reported SDQ scores in the borderline range. No differences were observed between TD and TD-no groups on any SDQ symptoms/problems or "somewhat true" PLEs.

Over two thirds of TD and TD-no children reported experiencing at least one "somewhat" true PLE. Among both TD and TD-no groups, the most frequently reported PLEs were beliefs regarding ability to read other people's minds, paranoid thoughts, and auditory hallucinations. Of note, paranoid thoughts and auditory hallucinations were also the most frequently endorsed PLEs among ASz and ASz-no children. In terms of PLEs, differences between ASz and TD children appear to be mainly due to the level of certainty and the impact of the experience as opposed to the frequency or type of PLE. No significant differences between TD and TD-no groups were observed for impact or distress.

Table 8. Percentages of TD (n=45) and TD-no (n=259) age 9 to 12 years reporting 'borderline' SDQ psychopathology and 'somewhat true' PLEs.

Antecedent	TD (%)	TD – no (%)	OR; p
Borderline SDQ scores			
Emotional symptoms (child reported)	4.5	6.2	0.8; 0.54
Conduct problems (caregiver reported)	13.6	6.6	2.3; 0.10
Hyperactivity-inattention (caregiver reported)	2.3	3.5	0.6; 0.62
Peer problems (caregiver reported)	9.1	7.3	1.2; 0.71
Psychotic like-experiences			
At least one 'somewhat true' PLE	79.5	86.1	0.7; 0.32
Have you ever heard voices that other people could not hear?	25.0	35.9	0.6; 0.21
Have you ever thought that you were being followed or spied upon?	43.2	55.0	0.6; 0.16
Have you ever seen something or someone that other people could not see?	18.2	22.9	0.8; 0.5
Have you ever known what another person was thinking even though that person wasn't speaking?	43.2	49.0	0.8; 0.52
Have you ever felt as though your body had been changed in some way that you could not understand?	13.6	26.3	0.4; 0.08
Do you have special powers that other people don't have?	9.1	13.9	0.6; 0.37
Have you ever felt that you were under the control of some special power?	6.8	10.4	0.7; 0.51
Have you ever believed that you were being sent special messages through the television?	9.1	13.9	0.6; 0.37
Some people believe that their thoughts can be read. Have other people ever read your thoughts?	20.5	26.6	0.7; 0.47
Do these experiences upset you? [a]	13.6	11.7	1.3; 0.74
Do these difficulties cause you difficulties at home or at school? [a]	0.0	15.0	N/A
Experiencing upset OR difficulties due to these experiences [a]	13.6	22.0	0.6; 0.35
Experiencing upset AND difficulties due to these experiences [a]	0.0	4.4	N/A

Notes: OR= odds ratio; and [a] Impact of PLEs were based on TD child reports of "somewhat-true" ratings and obtained from a smaller sample (TD n=29/TD-no n=205) due to earlier versions of screening questionnaires not containing questions on impact of PLE experiences.

Section 1: Cognitive abnormalities

Chapter 4 Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia

4.1 Introduction and aims of chapter

Evidence has accumulated to indicate that schizophrenia is, in part, a neurodevelopmental disorder (Murray and Lewis, 1987, Weinberger, 1987) characterised by abnormal functioning during childhood and adolescence (Niemi *et al.*, 2003, Schenkel and Silverstein, 2004). Converging evidence from prospective longitudinal studies of population cohorts, prospective studies of individuals at elevated risk of schizophrenia by virtue of having a family history of the illness, and from "follow-back" studies of adults with schizophrenia, suggest that cognitive and motor dysfunctions precede the onset of schizophrenia. However, past literature reviews of cognitive functioning among children who develop schizophrenia or SSD in adulthood have been limited in a number of respects: (i) they have focused exclusively on individuals with affected relatives (Keshavan *et al.*, 2010, Niemi *et al.*, 2003), or on population and/or birth cohorts (Khandaker *et al.*, 2011, Maccabe, 2008, Welham *et al.*, 2009a); (ii) they have not followed samples into adulthood and assessed them for schizophrenia or SSD; or (iii) they have included studies with estimated measures of premorbid intellectual functioning assessed in adulthood when the participant already had a diagnosis of schizophrenia (Schenkel and Silverstein, 2004). Thus, it remains unclear whether cognitive and motor deficits constitute robust antecedents of schizophrenia.

During childhood, individuals who subsequently developed schizophrenia or SSD, as compared to those who did not, were characterised by lower IQ (Woodberry *et al.*, 2008), and poorer motor function (Cannon *et al.*, 2002, Cannon *et al.*, 2006, Rosso *et al.*, 2000, Schiffman *et al.*, 2004, Walker *et al.*, 1994). Additional cognitive decline prior to the onset of the prodromal phase of schizophrenia has been reported (Bilder *et*

al., 2006, Fuller *et al.*, 2002, Maccabe *et al.*, 2013, Osler *et al.*, 2007). Scholastic achievement has also distinguished children who later developed schizophrenia or SSD, though findings have differed according to subject and assessment type (Bilder *et al.*, 2006, Crow *et al.*, 1995, Fuller *et al.*, 2002, Jones *et al.*, 1994, Maccabe *et al.*, 2007, Watt and Lubensky, 1976). Further, five studies reported no differences in premorbid scholastic performance (Ang and Tan, 2004, Cannon *et al.*, 1999, Helling *et al.*, 2003, Isohanni *et al.*, 1998, Isohanni *et al.*, 1999, Ullman *et al.*, 2012), which may reflect differences in the education systems characterising the study cohorts. Taken together, the extant literature suggests that individuals who develop schizophrenia present poorer cognitive abilities in childhood than those who never develop schizophrenia or SSD. Presently, little is known about the age at which these deficits emerge or their specific nature.

Two previous, widely cited, meta-analyses evaluated IQ among individuals who subsequently developed schizophrenia, and both yielded medium-sized deficits (Aylward *et al.*, 1984, Woodberry *et al.*, 2008). The present meta-analysis differs from the more recent of these, by Woodberry and colleagues, in several ways. Firstly, a number of studies that were included in that meta-analysis reported the results of IQ assessments completed at multiple ages spanning a broad age range of 3-19 years (Albee *et al.*, 1964, Cannon *et al.*, 2002, Cannon *et al.*, 2000, Jones *et al.*, 1994, Ott *et al.*, 1998, Seidman *et al.*, 2006a, Watt and Lubensky, 1976). An overall unweighted mean effect size was calculated for each of these studies spanning multiple assessments and a broad age range, thereby providing a less robust estimate of premorbid IQ than might be achieved by using a single assessment completed during childhood/adolescence. Secondly, the previous meta-analysis included studies of symptomatic, help-seeking individuals meeting inclusion criteria for treatment in an intervention programme for persons at ultra-high risk (UHR) for psychosis (Brewer *et*

al., 2005, Lencz *et al.*, 2006), and studies examining IQ among young adults (Kremen *et al.*, 2006, Lubin *et al.*, 1962, Reichenberg *et al.*, 2005, Whyte *et al.*, 2006, Zammit *et al.*, 2004). Given that intellectual deficits have been reported to increase in magnitude as psychosis onsets (Caspi *et al.*, 2003, Gunnell *et al.*, 2002, Rabinowitz *et al.*, 2000), the effect sizes of the difference between participants who did and who did not develop schizophrenia in these studies may reflect some early prodromal disease process rather than an antecedent of schizophrenia. Thirdly, while the previous meta-analysis included sub-analyses that examined IQ by narrower age bands, only three studies were included in the meta-analysis that assessed participants 13 years or younger. Finally, unlike both previous meta-analyses that focused solely on IQ (Aylward *et al.*, 1984, Woodberry *et al.*, 2008), the present meta-analysis includes examination of additional domains of scholastic achievement and motor functioning.

The aim of the present meta-analyses was to examine IQ, motor function, and scholastic achievement in children and young adolescents (aged ≤ 16 years) who subsequently developed schizophrenia or SSD. A recent review of studies on individuals at UHR for psychosis indicated a typical age of onset of basic prodromal symptoms of greater than 16 years (Ruhrmann *et al.*, 2010a). By restricting the meta-analyses to studies of children aged 16 years or younger, the present meta-analyses aimed to determine whether deficits in IQ, motor function, and scholastic achievement are present before the typical age of onset of the prodrome.

4.2 Methods

4.2.1 Sample

Meta-analyses were conducted to identify the effect sizes of differences in scores obtained on cognitive and motor performance measures by individuals aged 16 years or younger who subsequently developed schizophrenia compared to those who did not. Articles were identified via literature searches conducted in PUBMED/MEDLINE and

PsychINFO, using the keywords ‘schizophrenia’ and ‘IQ’ or ‘intelligence’ or ‘motor’ or ‘school’ or ‘scholastic’ and ‘premorbid’ or ‘prospective’ or ‘cohort’ or ‘high risk’. References from articles and relevant literature reviews were also examined for possible inclusion in meta-analyses. Inclusion criteria were: (1) written in English; (2) published or unpublished prospective investigations of birth cohorts or genetic-high risk samples, or follow-back investigations of population samples; (3) objective measures of cognitive or motor function when participants were aged 16 or younger; (4) results provided for cohort members who did and who did not develop schizophrenia or a SSD later in life; and (5) sufficient data to calculate effect sizes.

The initial literature search by the first author identified 3275 studies, of which 42 fulfilled the inclusion criteria. A co-author independently reviewed these studies to verify that inclusion criteria were met. Among the 42 studies, 14 contained samples that overlapped (Albee *et al.*, 1964, Cannon *et al.*, 2002, Cannon *et al.*, 2006, Cannon *et al.*, 2000, Crow *et al.*, 1995, Lane and Albee, 1963, 1968, Niendam *et al.*, 2003, Reichenberg *et al.*, 2010, Schiffman *et al.*, 2009, Schiffman *et al.*, 2004, Schulz *et al.*, 2012, Seidman *et al.*, 2006a, Seidman *et al.*, 2013). To avoid multiple entries on the same sample, only suitable data from the study containing the largest number of participants were analysed (Albee *et al.*, 1964, Cannon *et al.*, 2002, Cannon *et al.*, 2000, Crow *et al.*, 1995, Schiffman *et al.*, 2009, Seidman *et al.*, 2006a). Ten studies reported assessments of participants at multiple ages ranging from 3 to 19 years (Ang and Tan, 2004, Bilder *et al.*, 2006, Cannon *et al.*, 2002, Cannon *et al.*, 2000, Crow *et al.*, 1995, Jones *et al.*, 1994, Ott *et al.*, 1998, Rosso *et al.*, 2000, Watt and Lubensky, 1976, Welham *et al.*, 2009c). From these studies, only the results from a single assessment completed when participants were aged between 4 and 14 years old were included in the meta-analyses. Ten studies reported insufficient data to calculate an effect size (Ambelas, 1992, Cannon *et al.*, 1999, Cannon *et al.*, 2006, Crow *et al.*, 1995,

Erlenmeyer-Kimling *et al.*, 2000, Fuller *et al.*, 2002, Uggerby *et al.*, 2011, Ullman *et al.*, 2012, Venables and Raine, 2012, Walker *et al.*, 2002). Additional data from authors were obtained for all but five studies (Ambelas, 1992, Uggerby *et al.*, 2011, Ullman *et al.*, 2012, Venables and Raine, 2012, Walker *et al.*, 2002), but data from two studies remained insufficiently detailed to satisfy inclusion criteria (Erlenmeyer-Kimling *et al.*, 2000, Fuller *et al.*, 2002). Two other papers reported similar data (Isohanni *et al.*, 1998, Isohanni *et al.*, 1999); only data in the 1998 publication was included in the meta-analyses. Two studies that reported IQ scores for participants aged between 8 to 20 years old were excluded (Bower *et al.*, 1960, Sorensen *et al.*, 2006). Another study, which presented results for performance IQ between members of a rubella-exposed birth cohort who subsequently developed schizophrenia and those who did not, was also excluded from the meta-analysis (Brown *et al.*, 2001). A recent study examining verbal, spatial, and inductive ability at 13 and 18 years between male members of four Swedish birth cohorts who developed schizophrenia or SSD and those who did not was also excluded (Maccabe *et al.*, 2013).

Meta-analyses were performed using the results from the 22 studies that fulfilled inclusion criteria. Results were categorised into four domains of cognitive and motor function. Table 9 presents details of each study included in the meta-analyses, with a description of the sample, participant age at assessment, the test instrument used, and effect sizes denoting the difference in performance between the participants who subsequently developed schizophrenia or SSD compared to those who did not. Effect sizes were estimated using Cohen's *d*, obtained using sample sizes, means, and standard deviations (SD) for a group who later developed schizophrenia or a schizophrenia spectrum disorder and a comparison group, except where specified. Positive effect size values indicate better performance in the comparison group. Across all 22 studies, the age of the participants at the time of assessment ranged from 2 to 16 years. Twenty of

the 22 studies included males and females while three examined only males (Ang and Tan, 2004, Osler *et al.*, 2007). The comparison groups varied widely across studies, and were described as classmates, child psychiatric patients with no adult mental disorder, members of birth cohorts who did not develop schizophrenia or SSD, members of birth cohorts who did not develop any major mental disorder, and participants with or without a family history of schizophrenia or SSD.

Table 9. Study details and effect sizes for meta-analyses

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
IQ						
Albee *et al.*, (1964)	A follow-back study of adults from Cleveland, US	154 Schizophrenia patients recruited from hospital in-patient unit	4,166 children in same school year	11 – 12 years	Cleveland classification IQ test	0.64
Offord, 1976	A follow-back study of white adults from Pennsylvania, US	116 schizophrenia patients (including those with a diagnosis of mild to moderate retardation) recruited from in-patient unit. 51 males, 65 females.	116 school class mates matched on ethnicity, sex, and social class of origin. 51 males, 65 females.	During first 9 years of school (exact age not given)	Group administered IQ test	0.69[4]
Watt & Lubensky, (1976)	A follow-back study of adults from Massachusetts, US	36 schizophrenia patients recruited from hospital in-patient unit.	36 school classmates matched on sex, ethnicity and social class of origin	4 – 12 years	Kuhlman-Anderson IQ test/Otis self-administration test	0.49[5]

[4] Results were presented across gender, so data were collapsed and overall means and SD were used.

[5] Effect size was computed from the sample size and t-statistic.

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Jones *et al.,* (1994)	British birth cohort born 1946	30 cohort members with a diagnosis of schizophrenia. 20 males, 10 females	4,715 cohort members without schizophrenia. 2,457 males; 2,259 females.	11 years	Group administered IQ test	0.30[6]
Crow *et al.,* (1995)	British birth cohort born 1958	29 cohort members with a diagnosis of schizophrenia.	1446 cohort members with no psychiatric hospital admission	11 years	General ability IQ test	0.62[7]
Ott *et al*., (1998)	New York High-Risk project	18 study participants with a diagnosis of schizophrenia or SDD	189 study participants from a similar school district with no mental disorder in adulthood	7-12 years	WISC-R IQ	0.78
Cannon *et al*., (2000)	Birth cohort born between 1959-1966 from Philadelphia, US	57 cohort members with a diagnosis of schizophrenia or SSD. 41 males, 16 females	5,829 cohort members with no mental disorder in adulthood. 2,865 males; 2,964 females	7 years	WISC	0.53

[6] Effect sizes were taken from the Woodberry *et al.,* (2008) meta-analysis.

[7] Effect size was estimated from the sample size and f-statistic.

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Amminger *et al.,* (2000)	A follow-back study of adults born between 1960-1971 in Vienna	8 child psychiatric patients with a diagnosis of schizophrenia or SSD in adulthood.	13 child psychiatric patients with no diagnosis in adulthood.	16 years and younger	WISC	1.85
Cannon *et al.,* (2002)	Birth cohort born 1972-1973 from Dunedin, New Zealand	32 cohort members with a diagnosis of SSD	579 cohort members with no diagnosis of SSD, mania or anxiety/ depression	11 years	WISC	0.44
Seidman *et al.,* (2006)	Birth cohort born between 1959-1965 from New England, US	31 cohort members with a diagnosis of schizophrenia. 79.4% males, 20.6% females	61 cohort members with no diagnosis of SSD, bipolar disorder, recurrent depressive disorder, suicide attempts or psychiatric hospitalisations in adulthood. 54.8% males, 45.2% females.	7 years	WISC	0.65
Osler *et al.,* (2007)	Danish birth cohort of males born in 1953.	87 cohort members with a diagnosis of schizophrenia	6,790 cohort members who also completed a cognitive assessment at 18 years	12 years	Harnquist IQ test	0.14

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Welham *et al.*, (2009)	Birth cohort born between 1981-1984 from Brisbane, Australia.	53 cohort members with a diagnosis of non-affective psychosis.	3204 cohort members without a diagnosis of non-affective psychosis in adulthood.	14 years	Ravens Standard Progressive Matrices Test.	0.35[8]
Sorensen *et al.*, (2010)	Study participants drawn from Copenhagen Perinatal Cohort, individuals born 1959-1961	32 study participants with a diagnosis of SSD	133 study participants with no psychiatric diagnosis in adulthood.	10 – 13 years	WISC	0.45
Scholastic Achievement: General						
Isohanni *et al.*, (1998)	Northern Finland birth cohort 1966	84 cohort members with a diagnosis of schizophrenia. 54 males, 30 females	10,414 cohort members with no psychiatric hospital admission. 5,245 males; 5,169 females	16 years	School marks for all theoretical subjects	0.19

[8] Sample size for males and females were taken from measure of attentional dysfunction as not available for Raven's Standard Progressive Matrices Test. Effect size was calculated by converting beta to t-statistics (b/seB) with effect size derived from t-statistic and sample size for both males and females. A mean weighted effect size was then calculated based on sample size by gender.

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Cannon *et al.,* (1999)	Helsinki birth cohort born 1951-1960	400 cohort members with a diagnosis of schizophrenia or SSD	408 cohort members with a diagnoses other than schizophrenia	11 years	Year 4 examination results	0.02
Ang & Tan (2004)	A follow-back study of military servicemen from Singapore	30 military servicemen with a diagnosis of first-episode psychosis	30 military servicemen without a past or current mental disorder	12 years	Primary school leaving examination (average score)	-0.05
Bilder *et al.,* (2006)	A follow-back study of adults from New York	59 study participants with a diagnosis of schizophrenia or SDD recruited from a in-patient unit	26 study participants recruited from newspaper advertisements. No mental disorder and matched for sex and age	10-11 years	5^{th} grade achievement test results	0.53
MacCabe *et al.,* (2007)	Population-based historical cohort study of adults born 1973-1983 in Sweden	493 cohort members with a diagnosis of schizophrenia. 318 males, 175 females	713,876 cohort members with no diagnosis. 364,967 males; 348,909 females	15-16 years	Swedish National Examination grade point average	0.52

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Scholastic Achievement: Mathematics						
Jones *et al.*, (1994)	British birth cohort born 1946	30 cohort members with a diagnosis of schizophrenia. 20 males, 10 females	4,716 cohort members without schizophrenia. 2,457 males, 2,259 females	11 years	Group administered Maths test	0.41[9]
Crow *et al.*, (1995)	British birth cohort born 1958	29 cohort members with a diagnosis of schizophrenia.	1446 cohort members with no psychiatric hospital admission	11 years	Group Maths administered test	0.48[10]
Helling *et al.*, (2003)	A follow-back study of adults born in Sweden	59 study participants with a diagnosis of schizophrenia or SSD recruited from an in-patient unit	119 school classmates before/after each case alphabetically. Matched for gender, sex, age	12 years	End of year teacher assigned grades	0.14[6]
Ang & Tan, (2004)	A follow-back study of military servicemen from Singapore	30 military servicemen with a diagnosis of first-episode psychosis	30 military servicemen without a past or current mental disorder	12 years	Primary school leaving examination	0.33

[9] Sample sizes and f-statistics were used to calculate effect sizes.

[10] t-statistic was calculated from degrees of freedom and p-value given in paper, effect size was then estimated from sample size and t-statistic.

Study	Sample	Schizophrenia or SSD		Age at	Domain	Effect Size
		Present	Absent			
Motor Function						
Walker *et al.*, (1994)	A follow-back study of adults from Atlanta, US	30 schizophrenia patients recruited from hospital in- patient unit. 23 males, 7 females.	21 adults with no family history of mental disorders. 7 males, 14 females	2 – 15 years	Motor skills ratings (from childhood home videos)	0.39
Rosso *et al.*, (2000)	Birth cohort born between 1959-1966 from Philadelphia, US	66 cohort members with a diagnosis of schizophrenia or SSD.	6,473 cohort members with no mental disorder in adulthood.	7 years	Motor coordination test	0.48[11]
Cannon *et al.*, (2002)	Birth cohort born 1972-1973 from Dunedin, New Zealand	24 cohort members with a diagnosis of SSD	579 cohort members with no diagnosis of SSD, mania or anxiety/ depression	9 years	Basic Ability Motor Test	0.73
Schiffman *et al.*, (2009)	Study participants drawn from Copenhagen Perinatal Cohort, comprising of individuals born between 1959-1961	32 study participants with a diagnosis of schizophrenia	133 study participants with no mental disorder in adulthood	11-13 years	Motor coordination scale.	0.69

[11] To calculate the effect size the odds ratio was transformed into a Cohen's d using a method outline by Chinn, 2000.

4.2.2 Statistical Analyses

Meta-analyses were conducted with STATA (version 10; Stata Corporation, College Station, TX, USA) using a random effects model (Dersimonian and Laird, 1986) which assumes that the effects being investigated in a set of studies are a random sample drawn from a population of possible effect sizes. Meta-analyses were performed on difference scores for each domain of functioning, comparing participants who developed schizophrenia or SSD to those who did not. Difference scores were standardised by calculating Cohen's d effect sizes (Cohen, 1988) and interpreted according to effect size indices of "small (0.2)", "medium (0.5)", and "large (0.8)" (Cohen, 1992). The summary effect sizes for each domain were the standardised mean differences (SMD), weighted by the precision of the SMD. For each SMD, a z-value and significance level provided an indication of the two-sided statistical significance of the association at 95% probability level. For the IQ domain, the effect size from one study was an extreme outlier (Amminger *et al.*, 2000), so the analysis was conducted with and without this study included (Woodberry *et al.*, 2010).

The significance and magnitude of heterogeneity across studies were calculated using the Q statistic and I^2 statistic. Where there was significant heterogeneity within a domain, and where there were sufficient studies to provide adequate statistical power (i.e., for IQ only), effect size moderators were examined. Three potential moderator variables were examined: comparison group, IQ assessment instrument, and disorder outcome. Comparison group (matched comparison group or unselected cohort) was included as it had been reported to be a significant source of heterogeneity in a previous meta-analysis on IQ (Woodberry *et al.*, 2008). Instrument used to assess IQ (i.e., Wechsler Intelligence Scales or other test) was included as different types of IQ tests, particularly tests that are older, may provide variable estimates of IQ (Sattler, 2001). We

also examined disease outcome (i.e., schizophrenia or SSD) based on the rationale that individuals who develop schizophrenia may differ from those who develop SSD. For each variable, a regression model was estimated using an unrestricted maximum likelihood model. Publication bias was assessed graphically and statistically using published methods (Begg and Mazumdar, 1994, Egger *et al.*, 1997). In domains with five studies or less, publication bias could not be explored (Sutton *et al.*, 2000).

4.3 Results

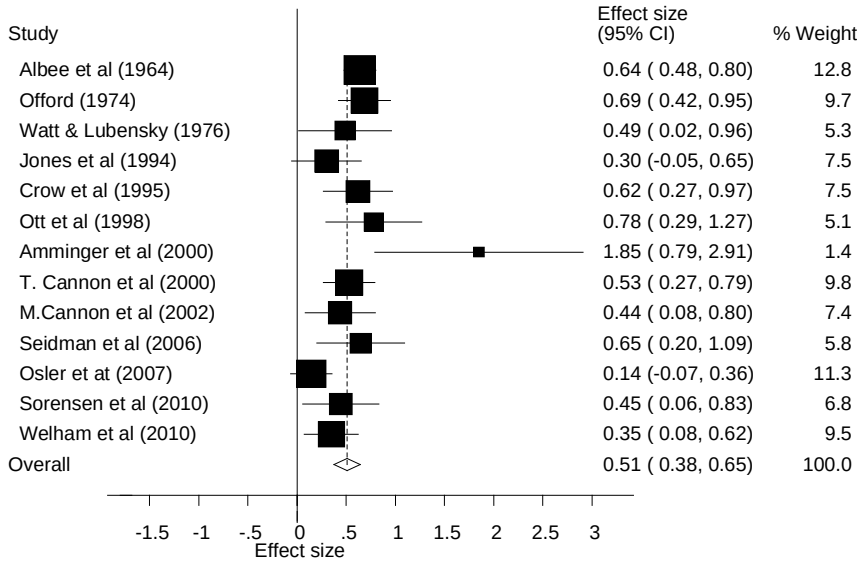
4.3.1 IQ

A meta-analysis of the 13 studies included in the IQ domain indicated that youth aged 16 years or younger who subsequently developed schizophrenia or SSD obtained lower IQ scores than youth who did not develop these disorders. As illustrated in Figure 2, a medium effect size was obtained (SMD = 0.51, [0.38, 0.65], z = 7.51, p<0.001). Significant heterogeneity was detected across studies (Q = 26.55, df = 12, p<0.05/I^2 = 54.8%), but neither comparison group, IQ measure, nor diagnostic outcome explained the heterogeneity. No publication bias was detected. After removing one study from the meta-analysis due to an effect size that was an outlier to the group (Amminger *et al.*, 2000), the observed effect size remained of medium magnitude (SMD = 0.49, [0.37, 0.61], z = 8.03, p<0.001). Significant heterogeneity was detected (Q = 20.25, df = 11, p<0.05/ I^2= 45.7%). Again, neither comparison group, IQ measure, nor diagnostic outcome was associated with heterogeneity.

The meta-analysis was repeated after excluding two studies that assessed participants between the ages of 14 and 16 years (Amminger *et al.*, 2000, Welham *et al.*, 2009c). All participants in the remaining 11 studies were aged 13 years or younger. This analysis yielded an effect size that was similar in magnitude to that calculated for participants aged 16 years or younger (SMD = 0.51, [0.38, 0.64], z = 7.69, p<0.001). As before, significant heterogeneity was detected (Q = 19.11, df = 10, p<0.05/ I^2 = 47.7%).

Again, heterogeneity was not associated with the type of comparison group, the measure of IQ, or the outcome diagnosis of schizophrenia or SSD. No publication bias was detected.

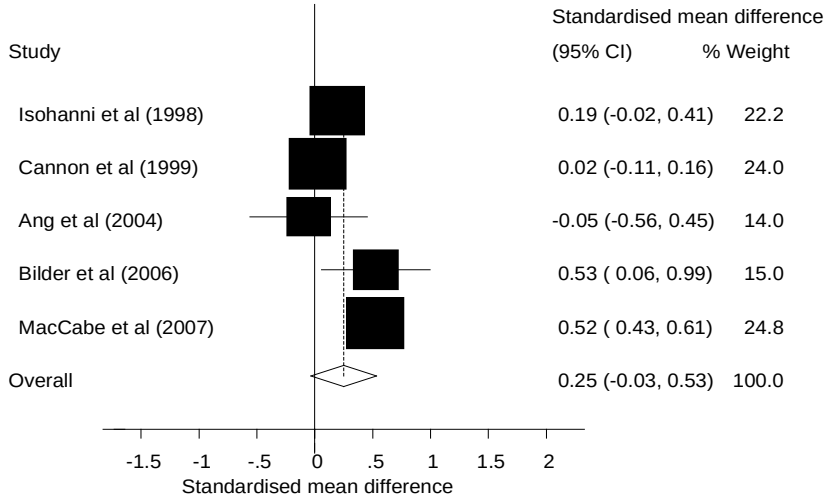
Figure 2. Forest plot for IQ



4.3.2 Scholastic Achievement: General

Five studies examined general scholastic achievement among youth aged 16 years or younger who subsequently developed schizophrenia or SSD, and the results indicated poorer overall scholastic achievement compared to youth who did not later develop schizophrenia or SSD (see Figure 3). However, the effect size of the group difference was small and non-significant (SMD = 0.25, [-0.03, 0.53], z =1.74, p = 0.08). Significant heterogeneity in the results was detected (Q = 40.72, df = 4, p<0.001/ I^2 = 90.2%), but could not be examined further given the limited number of studies comprising this domain.

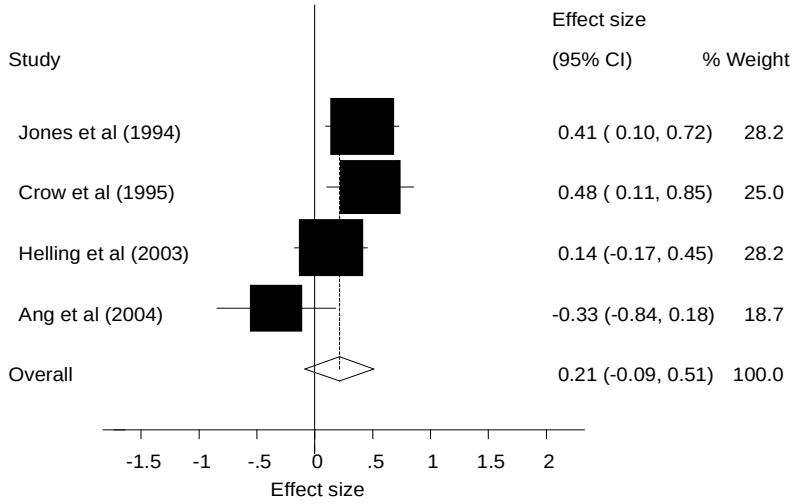
Figure 3. Forest plot for Scholastic Achievement: General



4.3.3 Scholastic Achievement: Mathematics

The results of the meta-analysis of four studies showed that, youth aged 16 years and younger who later developed schizophrenia or SSD, as compared to those who did not, achieved more poorly on tests of mathematics. However, as indicated in Figure 4, the effect size of the difference between the two groups was small and non-significant (SMD = 0.21, [-0.09, 0.51], z = 1.40, p = 0.16). Significant heterogeneity was detected (Q = 7.96, df = 3, p <0.05 / I^2= 62.3%), but could not be examined further due to an insufficient number of studies within the domain.

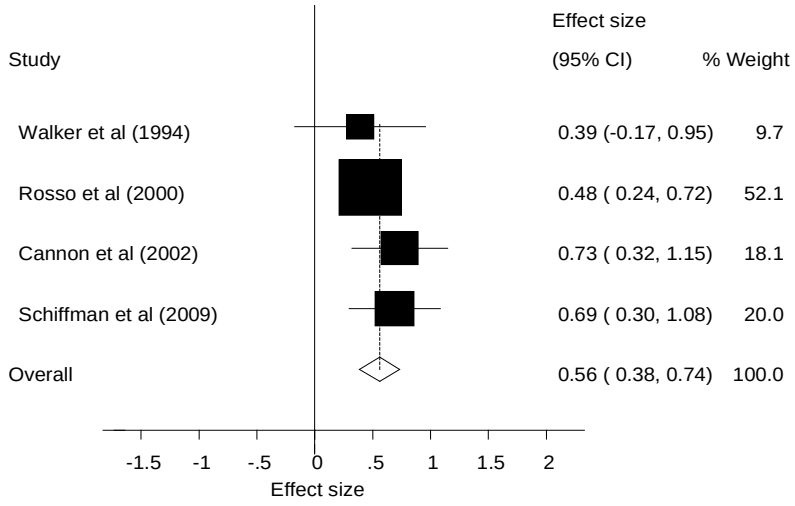
Figure 4. Forest plot for Scholastic Achievement: Mathematics



4.3.4 Motor Function

Of the four studies included in the motor function domain, the results from the meta-analysis showed that individuals aged 16 years or younger who subsequently developed schizophrenia or SSD, as compared to those who did not, displayed significant deficits in motor function (see Figure 5) that were moderate in size (SMD = 0.56, [0.38, 0.74], z = 6.25 p<0.001). No significant heterogeneity was detected across studies (Q = 1.87, df = 3, p = 0.60 / I^2 = 0.0%).

Figure 5. Forest plot for Motor Function



4.4 Discussion

To our knowledge, these are the first meta-analyses examining both cognitive and motor performance among youth aged 16 years or younger that later developed schizophrenia or SSD. The meta-analyses demonstrate that participants who subsequently developed schizophrenia or SSD displayed lower IQ and poorer motor function by age 16 than individuals who did not develop these disorders. Further, there were sufficient studies to conduct a meta-analysis that showed that the deficit in IQ was present by age 13. By contrast, overall scholastic achievement and performance on tests of mathematics did not significantly distinguish those who subsequently developed schizophrenia or SSD from those who did not. These results extend previous findings

by establishing that low IQ and impaired motor performance precede the prodrome and onset of illness.

While significant heterogeneity was detected in the meta-analyses of IQ and the two domains of scholastic achievement, the factors affecting heterogeneity could be examined only for IQ. Analyses indicated that heterogeneity reported for the IQ results was not due to the type of comparison group employed (matched comparison or unselected cohort), the test used to assess IQ (Wechsler or other), or to diagnostic outcome (schizophrenia or SSD).

The present meta-analyses obtained the same medium effect size for the difference in IQ by age 16, and by age 13 (d=0.51), between individuals who did and who did not develop schizophrenia or SSD later in life. The present IQ meta-analysis included results from five studies (Amminger *et al.*, 2000, Crow *et al.*, 1995, Osler *et al.*, 2007, Sørensen *et al.*, 2010, Welham *et al.*, 2009c) that had not been included in previous meta-analyses examining mean differences between future schizophrenia cases and comparison groups who did not develop schizophrenia (Aylward *et al.*, 1984, Woodberry *et al.*, 2008). Nevertheless, the effect sizes obtained in the present analyses by age 16 and by age 13 are similar in magnitude to that reported in a previous meta-analysis (d = 0.54) that included participants that were symptomatic or deemed to be at-risk for psychosis (Woodberry *et al.*, 2008). Thus, the present meta-analyses indicate that among individuals who later develop schizophrenia or SSD, a deficit in IQ is measureable by early to mid-adolescence.

Consistent with the findings of a previous meta-analyses (Woodberry *et al.*, 2008), the present analysis indicated that the specific measure of IQ employed did not account for significant heterogeneity in the results. Unlike the present meta-analysis, however, Woodberry and colleagues reported that the type of comparison group (i.e., unselected

cohort versus matched comparison group) accounted for significant effect-size heterogeneity. Their finding was attributed primarily to the inclusion of one study of 18 year old military conscripts that used an army classification battery to assess IQ (Lubin *et al.*, 1962).

It was not possible to examine all potential moderator variables in the meta-analysis of IQ. This was due to the relatively small number of studies that met inclusion criteria and the limited data available from each study. Examining a larger number of potential moderators may increase the likelihood of drawing false positive conclusions (Thompson and Higgins, 2002). Given evidence that the prevalence of schizophrenia is higher in males than in females (Aleman *et al.*, 2003a, Mcgrath *et al.*, 2004), it is possible that gender differences may have contributed to heterogeneity of results in the IQ domain, as reported in one previous meta-analysis (Aylward *et al.*, 1984), but not in another (Woodberry *et al.*, 2008). Unfortunately, the data available for inclusion in the present study were insufficient to permit statistical analysis of gender differences. Five studies included in the present meta-analysis reported the prevalence of schizophrenia separately by gender, and all but one (Welham *et al.*, 2009c) found higher rates among males than females (Cannon *et al.*, 2000, Jones *et al.*, 1994, Offord, 1974, Seidman *et al.*, 2006a). In these studies, the effect sizes of the differences in IQ of participants who did and who did not develop schizophrenia or SSD ranged from small to medium. Only two studies included in the present meta-analysis reported IQ scores separately for males and females (Offord, 1974, Welham *et al.*, 2009c). These studies indicated that among the participants who subsequently developed schizophrenia, the males obtained lower IQ scores than the females. However, we did not observe a larger effect size in the study that examined only males (Osler *et al.*, 2007) than in studies that included both males and females.

It is unclear whether lower than average IQ is an antecedent specific to schizophrenia. Lower than average IQ has been reported to characterise children (Koenen *et al.*, 2009, Van Os *et al.*, 1997) and young adults, particularly males (Tiihonen *et al.*, 2005, Urfer-Parnas *et al.*, 2009, Zammit *et al.*, 2004), who subsequently develop mental disorders other than schizophrenia. However, these findings are inconsistent and several studies have failed to identify IQ differences among children/adolescents who subsequently developed bipolar disorder (Cannon *et al.*, 2002, Reichenberg *et al.*, 2002, Zammit *et al.*, 2004).

Whether or not children and adolescents developing schizophrenia or SSD do poorly in school is currently unclear. Two recent reviews found that repeating a school year and achieving poor grades were associated with an increased risk of developing SSD (Maccabe, 2008, Welham *et al.*, 2009a) with some evidence identifying deficits in non-academic as opposed to academic subjects (Cannon *et al.*, 1999, Ullman *et al.*, 2012). The results of the present meta-analyses indicated no significant difference in either overall scholastic achievement or in performance on mathematics tests between individuals who did and did not later develop schizophrenia or SSD. This may be due, in part, to the inclusion of a study with a poorly-matched comparison group (Ang and Tan, 2004). In that study, the individuals who subsequently developed psychosis showed deterioration in mathematics test scores between age 12 to age 16 years. In the present meta-analysis, all of the participants in the studies that assessed performance in mathematics were aged 11 or 12 years. Furthermore, a study excluded from the Mathematics domain due to age of participants also found significant differences in mathematics achievement between individuals aged 12-18 years who did and did not develop schizophrenia in adulthood (Watt and Lubensky, 1976). It is possible that individuals who later develop schizophrenia or SSD display a decline in performance on mathematics tests after age 12. While significant heterogeneity was reported for both

domains of scholastic achievement, it could not be explored due to the limited number of studies meeting inclusion criteria. It is possible that the heterogeneity observed in the present meta-analysis, and the inconsistent results across studies, reflect differences in educational systems and measures of scholastic achievement that may preclude the examination of these domains in future meta-analyses.

The present meta-analysis indicated that by age 16 individuals who subsequently developed schizophrenia or SSD displayed poorer motor function than their peers who remained healthy. The lack of heterogeneity evidenced in this domain suggests that motor dysfunction is the most robust characteristic that distinguishes children/adolescents who subsequently develop schizophrenia. As previously noted, this is one of the most consistent findings in the literature on the antecedents of schizophrenia (Schenkel and Silverstein, 2004). Also consistent with these findings are the results of three studies, which could not be included in the present meta-analysis of motor function due to lack of available data (Crow *et al.*, 1995), or over-lapping samples (Cannon *et al.*, 2006, Schiffman *et al.*, 2004). These studies all reported deficits in motor function among children/adolescents aged 7 to 13 years who developed schizophrenia or SSD in adulthood. However, one study observed a reduction in motor dysfunction with increasing age among children who later developed schizophrenia, which may reflect the insensitivity of measures of motor function or age-related improvements in motor function similar to those reported among typically developing children (Walker *et al.*, 1994). In addition, one prospective study of a birth cohort that repeatedly assessed children did not detect motor function deficits at every age among those who later developed schizophreniform disorder (Cannon *et al.*, 2002). Given the relative paucity of prospective longitudinal studies that have assessed motor function through childhood and adolescence with repeated assessments, it is unclear whether

motor dysfunction is present across all periods of development among individuals developing schizophrenia or SSD.

4.4.1 Strengths and Limitations

The present study is characterised by two principal strengths. One, the meta-analyses included only studies that had assessed performance in youth aged 16 years or younger. None of the 22 studies included in the meta-analyses reported that they had assessed prodromal symptoms at the same time as they assessed cognitive and/or motor performance. However, given the participants age at the time of assessment, it is unlikely that the participants who subsequently developed schizophrenia or SSD had entered the prodromal phase of illness. Thus, the present results suggest that deficits in IQ and motor function emerge during childhood and early adolescence, prior to the onset of the prodrome. A second strength of the present meta-analyses was the examination of four domains of functioning: IQ, motor function, general scholastic achievement, and performance in mathematics tests. Only the IQ domain had been examined previously using meta-analytic techniques. Despite using broad search terms to identify relevant studies, only 22 studies met final criteria for inclusion in the present meta-analyses. This was primarily due to the limited number of studies of cognitive and motor function in youth aged 16 years or younger who subsequently developed schizophrenia or SSD. More evidence is needed. While the small number of studies precluded the examination of the heterogeneity of results obtained in domains other than IQ, the strict criterion requiring that participants had been assessed by age 16 allowed us to further understanding of the development of schizophrenia or SSD.

A potential caveat relates to the use of meta-analytic methods for comparisons of cognitive and motor function among children/adolescents of differing ages, which may fail to reflect the discontinuous nature of cognitive development (Harris, 1995). However, of the 22 studies included in the present meta-analyses, 19 assessed

participants at 13 years or under, and only six studies examined participants with an age-range of more than three years (Amminger *et al.*, 2000, Offord, 1974, Ott *et al.*, 1998, Sørensen *et al.*, 2010, Walker *et al.*, 1994, Watt and Lubensky, 1976). As only a few studies reported results separately for males and females, the meta-analyses could not contribute to the growing evidence on sex differences in the development of schizophrenia or SSD.

4.4.2 Conclusions

The meta-analyses provide evidence that among youth aged 16 years or younger who subsequently developed schizophrenia or SSD displayed lower IQ and poorer motor function than youth who did not develop illness. These results extend previous findings by showing that these deficits precede the onset of illness and of the prodrome. Furthermore, the results also endorse the view that schizophrenia, at least in part, represents a disorder of neurodevelopment. Stable cognitive and motor deficits in childhood and early adolescence are potential targets for interventions that may modulate illness development or reduce the extent of dysfunction present in individuals who develop schizophrenia or SSD.

Chapter 5 Literature review: Cognitive abnormalities among youth at-risk for schizophrenia

Aims of chapter

Research indicates that impaired cognitive abnormalities in childhood may index vulnerability to schizophrenia (Matheson *et al.*, 2011). The purpose of the following chapter is to clarify the extent to which cognitive impairments characterise youth at elevated risk for the development of schizophrenia. This review focuses on cross-sectional and longitudinal studies of cognitive performance among young non-ill relatives (i.e., < 30 years) of adults with schizophrenia, individuals meeting UHR criteria, and children and adolescents experiencing PLEs. Longitudinal studies examining cognitive impairments in relation to later transition to schizophrenia and/or psychosis among young relatives of adults with schizophrenia and UHR youth are also discussed.

5.1 Cognitive functioning

Neurocognitive dysfunction represents a core feature of the disorder that is largely independent of clinical symptoms, illness duration, and treatment (Reichenberg and Harvey, 2007). Among individuals with schizophrenia, cognitive dysfunction is predictive of functional outcome (Bowie et al, 2006), and represents a potentially treatable determinant of outcome. Adults with schizophrenia and individuals experiencing FEP are characterised by moderate-to-large effect size impairments in memory/learning, working memory, attention, processing speed, and EF (Dickinson *et al.*, 2007, Heinrichs and Zakanis, 1998, Mesholam-Gately *et al.*, 2009). Typically, cognitive performance among individuals with schizophrenia lies one to two standard deviations (SD) below that of age-matched comparison groups, and is lower than

expected based on maternal level of education (Keefe *et al.*, 2005, Keefe and Fenton, 2007).

Despite substantial heterogeneity in cognitive capacity among adults with schizophrenia, cognitive deficits appear to remain relatively stable among FEP samples and over the course of illness (Bora and Murray, in press, Rund, 1998). However, a recent meta-analysis examined data from eight studies assessing cognition in the same individuals longitudinally reported that cognitive performance may continue to decline after psychosis onset (Hedman *et al.*, 2013). While current pharmacological treatments do not appear improve cognitive impairments (Keefe *et al.*, 2011), cognitive rehabilitation has a positive effect (Wykes *et al.*, 2011).

Previous reviews have reported cognitive impairments during childhood and adolescence among individuals who later develop schizophrenia (Khandaker *et al.*, 2011, Maccabe, 2008, Niemi *et al.*, 2003, Schenkel and Silverstein, 2004, Welham *et al.*, 2009a, Woodberry *et al.*, 2008). Childhood cognitive deficits among individuals who develop schizophrenia in adulthood appear to be relatively stable (Cannon *et al.*, 2002, Cannon *et al.*, 2000, Crow *et al.*, 1995), but may be characterised by a slower rate of growth particularly for verbal abilities (Reichenberg *et al.*, 2010). However, a decrement in IQ, scholastic achievement, processing speed, learning, and executive function has been reported as these individuals pass through adolescence and approach early adulthood (Ang and Tan, 2004, Bilder *et al.*, 2006, Fuller *et al.*, 2002, Jones *et al.*, 1994, Maccabe *et al.*, 2013, Meier *et al.*, in press, Osler *et al.*, 2007, Seidman *et al.*, 2010). Thus, among individuals with schizophrenia, a decline in cognitive function has been reported to be present before and after illness onset (Hedman *et al.*, 2013, Meier *et al.*, in press).

The identification of cognitive precursors to schizophrenia has implications for the early identification and treatment of individuals at elevated risk for the development of schizophrenia. Moreover, given the association between cognitive function and functional outcomes both among individuals with schizophrenia and those meeting UHR criteria (Fett *et al.*, 2011, Green, 1996, Niendam *et al.*, 2006), cognitive rehabilitation may offer a means to ameliorate, delay or prevent onset of illness. The aim of this chapter is to establish whether cognitive and motor deficits constitute robust antecedents of schizophrenia. Table 10 at the end of the chapter provides details of studies examining cognitive functioning among individuals with a positive family history of schizophrenia or SSD aged 30 years or younger, youth meeting UHR criteria, and children and adolescents reporting PLEs. Effect sizes are presented for at-risk group relative to healthy comparison individuals only and were obtained from primary study or calculated using means and SDs provided unless specified (negative values indicate lower performance in at-risk group).

5.1.1 Individuals with a positive family history of schizophrenia or SSD

5.1.1.1 Cross-sectional studies

There is considerable evidence that unaffected adult relatives of individuals with schizophrenia also present substantial cognitive impairment relative to healthy comparison groups. Overall, unaffected first-degree adult relatives display deficits in attention, memory, EF, and processing speed with performance falling at an intermediate level between that of adults with schizophrenia and healthy adults (for reviews: Reichenberg and Harvey, 2007, Sitskoorn *et al.*, 2004, Snitz *et al.*, 2006, Szöke *et al.*, 2008, Trandafir *et al.*, 2006). These deficits are, however, less pronounced than those presented by schizophrenia patients.

The assessment of younger unaffected first- and second-degree relatives who have not yet passed through the typical age range of risk for schizophrenia (approximately

<30 years) provides the opportunity to explore cognitive dysfunctions that may be present prior to illness onset and could help identify risk factors for psychosis (Agnew-Blais and Seidman, 2013). Therefore, studies of unaffected relatives who have passed through the typical age of risk for schizophrenia have been excluded from the literature review (>31 years). Compared to unaffected adult relatives, young first- and second-degree relatives may include future cases, whereas older adult relatives will have a lower risk of developing schizophrenia or SSD. Therefore, cognitive impairments may be more severe among young relatives than among adult relatives (Seidman *et al.*, 2012).

Table 10 provides details of 25 cross-sectional studies examining cognitive functioning among unaffected relatives < 30 years. As described in Table 10, individuals with a positive family history of schizophrenia or SSD, as compared to healthy individuals, consistently present moderate-to-large effect size impairments in IQ, verbal working memory, verbal memory, verbal abilities as indexed by tests in word/reading comprehension, and EF (Barrantes-Vidal *et al.*, 2007, Bhojraj *et al.*, 2009, Byrne *et al.*, 2003, Chen *et al.*, 2009, Davalos *et al.*, 2004, De La Serna *et al.*, Delawalla *et al.*, 2006, Diwadkar *et al.*, 2011, Fis *et al.*, 2008, Hughes *et al.*, 2005, Keshavan *et al.*, 2010, Maziade *et al.*, 2008, O'connor *et al.*, 2009, Ozan *et al.*, 2010, Rutschmann *et al.*, 1980, Scala *et al.*, 2013, Schreiber *et al.*, 1992, Seidman *et al.*, 2006b). Although robust differences in IQ were identified in the majority of studies included in Table 10, it is not clear whether verbal IQ (verbal comprehension) or performance IQ (perceptual reasoning) may be relatively more impaired (Byrne *et al.*, 2003, Fis *et al.*, 2008, Schreiber *et al.*, 1992).

A number of studies included in Table 10 examined first-degree child and adolescent relatives of individuals with schizophrenia and also reported widespread cognitive impairment of moderate-to-large effect size in IQ, verbal memory, working

memory, verbal abilities, perceptual organisation, and EF (Davalos *et al.*, 2004, De La Serna *et al.*, 2010, Diwadkar *et al.*, 2011, Fis *et al.*, 2008, Klemm *et al.*, 2006, Ozan *et al.*, 2010, Rutschmann *et al.*, 1980, Schreiber *et al.*, 1992). Three early studies reported no differences in IQ among children of parents with schizophrenia aged 9 years or younger compared to children without a family history of the disorder (Cohler *et al.*, 1977, Landau *et al.*, 1972, Worland and Hesselbrock, 1980). Moderate effect size impairments between adolescents of parents with schizophrenia and adolescents of parents with no mental disorder aged 15 years have been reported for end of year school marks (Forsyth *et al.*, 2012, Jundong *et al.*, 2012). In line with previous meta-analyses, the magnitude of effect size differences in cognitive performance do not appear to vary between studies of siblings of individuals with schizophrenia or studies of offspring with a parent with the disorder (Snitz *et al.*, 2006), except for visual memory.

In contrast to cross-sectional studies of UHR individuals listed in Table 10, five studies reported visual memory deficits among FHx youth as compared to healthy comparison groups. Effect sizes for differences in performance on visual memory tasks were moderate in investigations of siblings and studies combining both first- and-second-degree unaffected relatives (Byrne *et al.*, 2003, Scala *et al.*, 2013), while large effect sizes were observed among adolescent offspring of a parent with schizophrenia (De La Serna *et al.*, 2010, Maziade *et al.*, 2008). Maziade and colleagues compared verbal and visual memory impairments in multigenerational families densely affected by schizophrenia and bipolar disorder and reported that verbal memory deficits characterised schizophrenia patients, unaffected adult relatives, and children of parents with schizophrenia compared to healthy comparison individuals (Maziade *et al.*, 2008). In contrast, visual memory impairments were observed only among adults with schizophrenia and offspring age 17 years of adults with schizophrenia. The authors suggested that while verbal memory may represent an inherited phenotype associated

with schizophrenia, visual memory may offer a better marker for risk of disease among young relatives of adults with schizophrenia (Maziade *et al.*, 2011b).

Twelve FHx studies included in Table 10 examined the domain of attention; however, only three studies reported poorer attention among young relatives of adults with schizophrenia or SSD compared to healthy individuals. Of these three studies, two included youth with affected first- and second-degree relatives (Barrantes-Vidal *et al.*, 2007, Keshavan *et al.*, 2010), and one examined children aged 12 years with a parent with the disorder (Schreiber *et al.*, 1992). One study reported spatial working memory impairment among adult siblings of individuals with schizophrenia (Barrantes-Vidal *et al.*, 2007). To date, it is not clear whether attention and spatial working memory impairments characterise FHx youth; however, inconsistencies in results may be due to differences in task characteristics and/or memory load (Reichenberg and Harvey, 2007, Seidman *et al.*, 2012).

Relative to cross-sectional studies of youth meeting UHR criteria, only a small number of studies of relatives of persons with schizophrenia or SSD included a measure of processing speed. As with UHR studies, there appears to be little consistency regarding cognitive measures included in EF and processing speed domains. Nevertheless, of the three studies of first- and second-degree relatives of individuals with schizophrenia that included the 'Digit Symbol Substitution Test' (DSST) (Wechsler, 1997, 2003), two reported moderate effect size differences between FHx youth and a healthy comparison group (Byrne *et al.*, 2003, Schreiber *et al.*, 1992).

Thus far, youth with a positive family history of schizophrenia or SSD are characterised by widespread intellectual and cognitive impairments compared to healthy youth. With the exception of visual memory, impairments do not appear to be of greater severity among studies of young children and adolescents of individuals with

schizophrenia or SSD as compared to studies of young adult siblings of individuals with the disorder.

Investigations that include both unaffected first- and -second- degree relatives of individuals with schizophrenia (Bhojraj *et al.*, 2009, Byrne *et al.*, 2003, Keshavan *et al.*, 2010, O'connor *et al.*, 2009) did not report smaller effect size differences relative to those studies examining only first-degree relatives. This is in contrast to findings from investigations of unaffected adult relatives, which indicate that the degree of neurocognitive impairment may be associated with the degree of familial loading for the disorder, as indexed by degree of relatedness to affected individuals, with higher familial loading being associated with greater levels of neurocognitive impairment (Cannon *et al.*, 2000, Faraone *et al.*, 2000, Gur *et al.*, 2007, Tsuang *et al.*, 2006, Tuulio-Henriksson *et al.*, 2003, Zilles *et al.*, 2009). More recently, Keshavan and colleagues reported that among youth aged 10 to 25 years, neurocognitive deficits were more severe among those individuals with an affected first-degree relative than in individuals with a second-degree relative (Keshavan *et al.*, 2010). At present, it is not clear whether the severity and breadth of neurocognitive impairments vary by closeness of the affected relatives among youth who have not yet reached the age-range of illness onset.

5.1.1.2 Longitudinal studies examining a single cognitive assessment in relation to later schizophrenia

A few prospective longitudinal investigations of young relatives of adults with schizophrenia assessed cognitive function only once during childhood and adolescence and followed these individuals into adulthood. Results of these studies indicate that low IQ, poor scholastic achievement, verbal ability, attention, verbal memory, and working memory assessed during childhood is associated with later schizophrenia (Erlenmeyer-Kimling *et al.*, 2000, Seidman *et al.*, 2013, Sorensen *et al.*, 2006). These studies are not included in Table 10 but are discussed in more detail in Chapter Four of the thesis.

5.1.1.3 Longitudinal studies examining repeated assessments of cognitive function

As shown in Table 10, a number of studies have explored changes in cognitive function over time among unaffected relatives aged <30 years. One study reported a decline in verbal IQ between age 5 and 16 among the offspring of schizophrenia patients (Worland *et al.*, 1982). Furthermore, relative to a healthy comparison group, unaffected relatives aged 16 to 25 years displayed deficits in IQ, processing speed, verbal memory, and EF that were stable over a two year period (Cosway *et al.*, 2000). In addition, stable impairments in verbal working memory between 9 and 12 years have also been demonstrated among offspring of a parent with schizophrenia as compared to children without a parent with schizophrenia assessed only once at 11 years (Ross *et al.*, 2008). A more recent investigation of siblings and offspring of adults with schizophrenia aged 15 years observed improvements in attention, but a stable deficit (non-significant decline) in EF performance from baseline performance to one year and two year follow-up assessments compared to a typically-developing group of similar age (Bhojraj *et al.*, 2010). A lack of significant differences in EF performance has also been reported over a 10 year period among young unaffected adult siblings compared to a healthy comparison group (Sánchez-Torres *et al.*, 2013).

5.1.1.4 Longitudinal studies examining multiple cognitive assessments in relation to later schizophrenia

Available evidence from prospective longitudinal investigations that have examined cognitive function at repeated assessments and followed young relatives of adults with schizophrenia into adulthood indicate a stable IQ deficit between 7 and 9 years among offspring of adults with schizophrenia who later developed schizophrenia (Ott *et al.*, 1998). Stable verbal memory impairment was also reported among older first- and second-degree unaffected relatives compared to healthy comparison group (Whyte *et*

al., 2006). These studies are not included in Table 10 but are discussed in more detail in Chapter Four of the thesis.

5.1.2 Symptomatic, help-seeking individuals meeting Ultra High-Risk criteria

5.1.2.1 Cross-sectional studies

Although findings from the 15 cross-sectional studies of youth meeting UHR criteria listed in Table 10 are by no means consistent, there is evidence of cognitive impairments in attention, spatial working memory, verbal working memory, and verbal memory compared to healthy individuals (Bartók *et al.*, 2005, Carrion *et al.*, 2011, Frommann *et al.*, 2011, Gschwandtner *et al.*, 2003, Hawkins *et al.*, 2004, Kim *et al.*, 2011, Lindgren *et al.*, 2010, Niendam *et al.*, 2006, Özgürdal *et al.*, 2009, Pflueger *et al.*, 2007, Pukrop *et al.*, 2006, Simon *et al.*, 2007, Smith *et al.*, 2006). Notably, there were no studies of UHR individuals that evaluated scholastic performance possibly due to the age of participants. Visual memory was examined in four studies only, none of which observed differences between UHR and comparison groups (Hawkins *et al.*, 2004, Kim *et al.*, 2011, Niendam *et al.*, 2006, Pukrop *et al.*, 2006).

IQ appears to be relatively spared with only two studies reporting differences between individuals who did and did not meet UHR criteria (Özgürdal *et al.*, 2009, Pflueger *et al.*, 2007). A previous review also reported no impairment in IQ despite widespread neurocognitive dysfunction which may reflect methodological differences across studies and matching of UHR and comparison groups on general intellectual ability (Brewer *et al.*, 2006). Alternatively, among individuals meeting UHR criteria, those who seek care and are thereby recruited into studies, may present higher IQ. This may be one of the reasons for their help-seeking behaviour.

There was some overlap across studies in measures of EF and processing speed. Different studies include identical tests in different cognitive domains, or assess the

same domain using different tests (Pukrop and Klosterkötter, 2010). Ten studies included in Table 10 reported EF deficits assessed using a diversity of measures tapping different higher cognitive functioning abilities, that is, abstraction, planning, problem solving, cognitive flexibility, and response inhibition among UHR youth (Carrion *et al.*, 2011, Frommann *et al.*, 2011, Gschwandtner *et al.*, 2003, Hawkins *et al.*, 2004, Kim *et al.*, 2011, Lindgren *et al.*, 2010, Özgürdal *et al.*, 2009, Pflueger *et al.*, 2007, Pukrop *et al.*, 2006). The assessment of EF is made difficult because these abilities depend on functioning of networks rather than on frontal brain regions (Eisenberg and Berman, 2009) and on lower order abilities such as memory and attention. Thus, whilst there is considerable evidence for EF impairment among UHR youth it is not clear if this relates to a specific executive ability or reflects difficulties in basic cognitive abilities.

Meta-analyses of cognitive functions among adults with schizophrenia (Dickinson *et al.*, 2007) and UHR individuals (Fusar-Poli *et al.*, 2012b) identified processing speed impairments using the DSST measure. Consistent with these findings, four out of five cross-sectional studies that included the DSST in the processing speed domain all reported significant differences between UHR individuals relative to comparison groups (Carrion *et al.*, 2011, Hawkins *et al.*, 2004, Niendam *et al.*, 2006).

Overall, UHR individuals exhibit widespread cognitive impairment in the presence of relatively preserved general intellectual ability. On average, impairments on cognitive domains between individuals who did and did not meet UHR criteria ranged from small to moderate in effect size. Cross-sectional data also indicates that cognitive deficits may increase in severity with the emergence of prodromal symptomology (Pukrop and Klosterkötter, 2010). Indeed, individuals identified as being in an “early” UHR phase (based on BS criteria) were less cognitively impaired than individuals in a “late” UHR phase based on SIPS/CAARMS criteria described in Chapter One (Frommann *et al.*, 2011, Pukrop *et al.*, 2006, Simon *et al.*, 2007). Findings from these

three studies suggest that verbal memory is the most severely affected domain and may be a marker of disease progression among UHR youth (Frommann *et al.*, 2011).

Typically, the cognitive impairments among UHR individuals described in Table 10 were less marked than those observed among individuals experiencing FEP (Broome *et al.*, 2007, Kim *et al.*, 2011, Özgürdal *et al.*, 2009, Pukrop *et al.*, 2006, Simon *et al.*, 2007). Further, meta-analyses of cross-sectional studies of cognitive function among youth who subsequently developed schizophrenia and in FEP individuals suggest that cognitive functioning may decline during the phase when psychosis emerges and/or after illness onset (Khandaker *et al.*, 2011, Mesholam-Gately *et al.*, 2009, Woodberry *et al.*, 2008). This decline in cognitive functioning may reflect changes in the frontal and temporal lobes during transition to psychosis (Pantelis *et al.*, 2003). Based on the available evidence it is not clear whether cognitive deficits reflect difficulties associated with current symptoms or a stable, underlying trait specifically associated with schizophrenia. Longitudinal studies examining cognitive function on repeated occasions are needed to establish a relationship with the course of illness.

5.1.2.2 Longitudinal studies examining a single cognitive assessment in relation to transition to psychosis

A number of studies of youth meeting UHR criteria have examined the predictive utility of cognitive ability assessed at one point in time among individuals who transition to psychotic illness compared to UHR individuals who do not transition. These studies are not described in Table 10 but allow for the identification of cognitive factors associated with UHR status (similar to cross-sectional investigations), but also to the later conversion to psychosis. Overall, UHR individuals who later convert to psychosis compared to those who do not are characterised by more severe impairments based on a single cognitive assessment (Eastvold *et al.*, 2007, Pukrop and Klosterkötter, 2010, Seidman *et al.*, 2010).

Transition to psychosis appears to be associated with poor verbal memory performance (Brewer *et al.*, 2005, Eastvold *et al.*, 2007, Lencz *et al.*, 2006, Lin *et al.*, 2011, Simon *et al.*, 2012, Woodberry *et al.*, 2010) and verbal IQ (Eastvold *et al.*, 2007, Pukrop *et al.*, 2007, Woodberry *et al.*, 2010). Other cognitive predictors of illness have been identified, though less consistently; namely, verbal ability (Seidman *et al.*, 2010), visual memory (Lin *et al.*, 2013), working memory and processing speed (Pukrop *et al.*, 2007), and EF impairments (Koutsouleris *et al.*, 2012). Two studies reported no significant differences between UHR individuals who did and did not convert to psychosis on measures of attention (Francey *et al.*, 2005) and memory (Wood *et al.*, 2003).

In line with evidence from cross-sectional studies, longitudinal investigations of cognitive functioning among UHR youth suggest that verbal memory impairments may be a marker of disease progression. Evidence from a recent meta-analysis also found that in addition to the cognitive impairments detailed above, significantly lower IQ characterised UHR individuals who transitioned to psychosis compared to those UHR individuals who did not (Fusar-Poli *et al.*, 2012b). However, findings from the longitudinal studies included in Table 10 must be interpreted with caution as the majority of studies include only a small number of UHR individuals (< 20) that transition to psychosis (Eastvold *et al.*, 2007, Koutsouleris *et al.*, 2012, Lencz *et al.*, 2006, Simon *et al.*, 2012, Woodberry *et al.*, 2010). Therefore, further studies employing larger UHR sample sizes are needed before cognitive markers of disease progression can be confirmed.

5.1.2.3 Longitudinal studies examining repeated cognitive assessments

To date, few studies have examined the repeated measurement of cognitive function among UHR youth. Six longitudinal studies included in Table 10 examined the short-term progression, with follow-up periods from 6 to 18 months, among UHR individuals

compared to healthy comparison groups. Results generally indicated improvement across all cognitive domains particularly in IQ (Barbato *et al.*, 2013, Jahshan *et al.*, 2010, Niendam *et al.*, 2007, Woodberry *et al.*, 2013), which theoretically could be due to practice effects (Goldberg *et al.*, 2010) or treatments (Niendam *et al.*, 2007). However, a decline in performance among UHR youth compared to healthy individuals has been reported on verbal working memory (Niendam *et al.*, 2007, Woodberry *et al.*, 2013), verbal working memory and EF (Jahshan *et al.*, 2010), processing speed and verbal fluency (Keefe *et al.*, 2006), and verbal memory and verbal fluency (Barbato *et al.*, 2013). One study reported no differences in performance on a spatial working memory task of UHR individuals compared to healthy individuals assessed over a one year interval (Fusar-Poli *et al.*, 2010). However, recent meta-analyses of longitudinal cognitive function among individuals with FEP and studies of individuals meeting UHR criteria found no evidence for a cognitive decline among UHR youth (Bora and Murray, in press).

5.1.2.4 Longitudinal studies examining repeated cognitive assessment in relation to transition to psychosis

A decline in cognitive functioning based on repeated measurements that is predictive of transition to psychosis among UHR individuals has implications for earlier, targeted interventions. These studies may potentially identify risk and protective factors that influence onset, severity and course of illness. Although these studies are relatively few, there is some evidence to indicate that a deterioration in verbal memory, visual memory, working memory, and processing speed characterise UHR youth who transition to psychosis compared to UHR youth who did not (Jahshan *et al.*, 2010, Wood *et al.*, 2007, Woodberry *et al.*, 2013), though these findings are not consistent with two studies reporting no differences (Becker *et al.*, 2010, Hawkins *et al.*, 2008). Moreover, meta-analyses of studies of longitudinal cognitive function among

individuals meeting UHR criteria found no evidence of a cognitive decline among UHR youth who transitioned to psychosis compared to UHR youth who did not transition (Bora and Murray, in press). Given that the majority of UHR individuals are already young adults when prodromal symptoms emerge, it is not clear when cognitive deficits onset and/or the decline begins.

5.1.3 Studies comparing individuals with a positive family history and youth meeting Ultra High-Risk criteria

To date, three studies have compared performance of individuals with a positive family history of schizophrenia or SDD and youth meeting UHR criteria on an extensive neurocognitive test battery (Mukkala *et al.*, 2011, Myles-Worsley *et al.*, 2007, Seidman *et al.*, 2010). Seidman and colleagues reported significant global impairment among both first- and second-degree FHx youth and UHR youth relative to a healthy comparison group. On specific subtests, impairments were observed on measures of verbal comprehension, processing speed, and verbal fluency among the FHx group relative to healthy individuals, while those meeting UHR criteria performed more poorly than the healthy comparison group on tests of processing speed, verbal learning, and memory. Direct comparisons of performance of the two risk groups revealed significant differences between FHx and UHR youth only on tests of verbal memory, with UHR individuals exhibiting significantly greater impairment (Seidman *et al.*, 2010). Further, poorer verbal memory scores predicted more rapid transition to psychosis in the UHR group (Seidman *et al.*, 2010).

Another investigation found that first- and second-degree FHx youth aged between 14-19 years displayed impaired verbal memory, verbal working memory, attention, and motor function, while UHR individuals of a similar age were impaired on spatial working memory and perceptual organization (Myles-Worsley *et al.*, 2007). By contrast, a recent study reported no differences in neurocognitive functioning between

young adult offspring with a parent with schizophrenia or SSD and UHR individuals relative to a healthy comparison group (Mukkala *et al.*, 2011). The results of these studies are consistent with findings from cross-sectional UHR and FHx studies described in Table 10 which indicate differing profiles of neurocognitive impairment in FHx and UHR individuals.

5.1.4 Studies of children experiencing psychotic like-experiences

Overall (see Table 10), youth reporting PLEs exhibit differences of moderate effect size in IQ and scholastic achievement relative to youth with no PLEs (Bartels-Velthuis *et al.*, 2011, Horwood *et al.*, 2008, Polanczyk *et al.*, 2010). Low IQ may reflect a non-specific risk factor for later mental disorders as does the presence of PLEs (Fisher *et al.*, in press, Koenen *et al.*, 2009). Nonetheless, the IQ impairment of moderate effect size reported in studies described in Table 10 is similar in magnitude to that observed during childhood and adolescence among individuals who subsequently develop schizophrenia compared to individuals who do not (Woodberry *et al.*, 2008).

One group of investigators did not observe differences in IQ/scholastic achievement between youth who did and did not report PLEs at interview (Blanchard *et al.*, 2010, Kelleher *et al.*, 2012c). Using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS: Nuechterlein *et al.*, 2008) battery in a larger sample (n=165) than reported previously in the same group (Blanchard *et al.*, 2010), Kelleher and colleagues observed impairments in processing speed and non-verbal working memory among adolescents aged 11 to 13 years with PLEs compared to adolescents not reporting PLEs at clinical interview (Kelleher *et al.*, 2012c). Although these effect sizes were small-to-moderate in magnitude, results are consistent with studies of adults with schizophrenia indicating that slowed processing speed is a core deficit in schizophrenia (Carrion *et al.*, 2011, Dickinson *et al.*, 2007, Rodríguez-Sánchez *et al.*, 2007). These findings are also congruent with evidence from a

prospective longitudinal cohort study indicating that deficits in processing speed at age 13 years were associated with increased risk for psychotic disorders in adulthood (Cannon *et al.*, 2006).

Recently, one study reported findings from a large British birth cohort (n = 6,784) on the development of cognitive function among children reporting PLEs (Niarchou *et al.*, 2013). This study examined processing speed, reasoning and problem solving, attention/vigilance, and working memory at 8 and 10/11 years among children who reported experiencing PLEs at 12 years compared with children of the same age that did not. Results of this study indicate that lower performance on measures of processing speed (age 8), attention (ages 8 and 11), and working memory (ages 8 and 10), as well as improvement in processing speed between the ages of 8 and 11 years, were associated with PLEs at 12 years (Niarchou *et al.*, 2013). Slower processing speed at 8 years among children reporting PLEs is consistent with previous work by other groups (Kelleher *et al.*, 2012c). The observed improvement in processing speed from 8 to 11 years may reflect a delay in the normal development of processing speed among children reporting PLEs in childhood (Niarchou *et al.*, 2013). Results from the same birth cohort also indicate that a decline in literacy skills between 7 and 9 years was associated with PLEs at 12 years (Hameed *et al.*, 2013).

5.1.5 Summary

There is evidence of heterogeneous cognitive deficits among FHx youth, individuals meeting UHR criteria, and children/adolescents reporting PLEs, though low IQ, poor memory, EF, and processing speed appear to be relatively robust findings. Disparity in results may be due to some extent to identical tests being used to index different cognitive domains, particularly the domains of EF and processing speed. Methodological differences across studies make it difficult to aggregate results. Inconsistency between findings may also reflect the wide age-range of the individuals

studied, and the differing degrees or definitions of risk employed across studies. That is, UHR individuals tend to be older and closer to transition to illness, while studies of FHx individuals typically examine first- and second-degree relatives of adults with schizophrenia in childhood, adolescence, and adulthood. If schizophrenia is a neurodevelopmental disorder, it is plausible that distinctive patterns of deficits are present at different ages.

Nonetheless, extant literature indicates that cognitive dysfunctions are present prior to onset of schizophrenia among youth at elevated risk for the disorder relative to typically developing peers. However, a number of questions remain unanswered. Firstly, among children presenting with antecedents of schizophrenia and children with a positive family history of schizophrenia or SSD it is not clear whether cognitive impairments tap corresponding domains of similar severity. Secondly, although low IQ is prominent among at-risk groups and associated with conversion to psychosis in UHR youth, the extent to which specific cognitive impairments reflect generalised intellectual difficulties, as indexed by standardised intelligence batteries, has not been established. Thirdly, among those who are at-risk by virtue of family history, the severity and diversity of impairments may vary according to the closeness of the relationship to affected relatives. Fourthly, due to the relative paucity of longitudinal studies examining the developmental course of cognitive impairments prior to the age associated with onset of prodromal symptoms, it is not known whether children presenting with antecedents of schizophrenia and children with a positive family history of schizophrenia or SSD exhibit distinct cognitive trajectories over time. Chapters Six and Seven of this thesis will attempt to address these questions.

Table 10. Descriptions of studies examining cognitive performance

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Cross-sectional studies of individuals with a positive family history					
Landau et al, (1972)	131 offspring of parents with schizophrenia (Sz-O) and 124 health comparison individuals (Comp)	Not specified but over 5 years	IQ	No differences between groups	
Cohler *et al.*, (1977)	24 Sz-O and 33 Comp	5 yrs	IQ and attention	No differences between groups	
Worland and Hesselbrock (1980)	94 Sz-O and 119 Comp	Sz-O (9yrs) / Comp (9 yrs)	IQ	No difference in between groups	
Rutschmann *et al.*, (1980)[12]	46 Sz-O and 53 Comp	Sz-O (16 yrs) / Comp (15 yrs)	Working memory	Significant differences between Sz-O and Comp group	Working memory: total words, *d* =-0.52; total, *d* =-0.48
Schreiber *et al.*, (1992)[13]	23 Sz-O and 61 Comp	Sz-O (12yrs) / Comp (12 yrs)	IQ, attention, and processing speed	Significant differences between Sz-O and Comp group for IQ, verbal IQ, attention and processing speed	IQ: full IQ, *d* =-0.58; verbal IQ, *d* =-0.56 Attention: *d* =-0.48 Processing speed: *d* =-0.56

[12] Effect size taken from Agnes-Blais and Seidman (2012)
[13] Effect size taken from primary paper except for processing speed domain

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Davalos *et al.*, (1994)	51 Sz-O and 51 Comp	Sz-O (10 yrs) / Comp (10 yrs)	Verbal abilities, working memory, visuospatial processing, and executive function (EF)	Sz-O poorer performance on verbal abilities and EF	Verbal abilities: *d* =-0.77 EF: *d* =-0.82
Byrne *et al.*, (2003)	157 1st and 2nd degree relatives of individuals with schizophrenia (Sz-R) and 34 Comp	Sz-R (21 yrs) / Comp (21 yrs)	IQ, processing speed, memory/learning, attention, verbal ability/language, mental control/encoding and EF	Sz-R had lower IQ, processing speed, verbal ability, verbal learning and memory, and visual memory compared to Comp	IQ: verbal IQ, *d* =-0.53; performance IQ, *d* =-0.54; full-scale IQ, *d* =-0.59 Processing speed: digit span, *d* =-0.53; speed comprehension, *d* =-0.44 Verbal ability: *d* =-0.52 Verbal learning: *d* =-0.65 Verbal memory: immediate story recall, *d* =- 0.56; delayed story recall, *d* =-0.65 Visual memory: immediate recall, *d* =-0.65; delayed recall, *d* =-0.58
Hughes *et al.*, (2005)	25 siblings of schizophrenia patients (Sz-S), 25 individuals with schizophrenia (Sz), and 25 Comp	Sz-S (28 yrs) / Sz (29 yrs) / Comp (28yrs)	IQ, memory/learning, attention, visual-spatial abilities, and EF	Sz-S lower IQ and EF (category fluency only) relative to Comp but Sz lower performance overall	IQ: *d* =-0.66 EF: category fluency, *d* -= 0.73

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Schubert and McNeil (2005)	28 Sz-O and 88 Comp	Sz-O (22 yrs) / Comp (22 yrs)	Verbal memory, attention, grammatical reasoning, motor speed, and EF	Sz-O lower verbal memory, attention, and grammatical reasoning relative to Comp	Insufficient data calculate effect sizes
Delawella *et al.*, (2006)	31 Sz-S, 27 Sz, 39 Comp, and 42 siblings of healthy comparison individuals (Comp-S)	Sz-S (20 yrs) / Sz (22 yrs) / Comp (21 yrs) / Comp-S (20 yrs)	Episodic memory, working memory, attention, and EF	Sz-S significantly worse on measures of episodic memory, working memory and EF compared to Comp-S group. Sz impaired on all domains relative to Comp	Insufficient data calculate effect sizes
Klemm *et al.*, (2006)	32 siblings and offspring of individuals with schizophrenia (Sz-S/O) and 32 Comp	Sz-S/O (16 yrs) / Comp (16 yrs)	EF	Compared to Comp group, Sz-S/O were impaired on some EF measures (see effect sizes)	EF[14]: WCST correct trials, *d* =-0.75, errors, *d* =-0.61, complete categories, *d* =-0.52; Stroop time, *d* =-0.65, errors, *d* =-0.9; TMT-A, *d* =-0.74; TMT-B, *d* =-0.77
Seidman *et al.*, (2006)	73 Sz-S/O and 84 Comp	Sz-S/O (18 yrs) / Comp (16 yrs)	Verbal ability, verbal memory/learning, visuo-spatial ability, processing, working memory, and EF	Sz-S/O significantly poorer on verbal ability and EF compared to comp	Verbal ability: vocabulary, *d* =-0.73; reading, *d* =-0.57EF: verbal fluency *d* =-0.37

[14] WCST= Wisconsin Card Sorting Test; TMT-A= Trial Making Test A; and TMT-B= Trial Making Test B

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Barrantes-Vidal *et al.*, *(*2007)	38 Sz-S, 68 Sz, and 63 Comp	Sz-S (27 yrs) / Sz (25 yrs) / Comp (25yrs)	IQ, spatial working memory, attention, verbal memory, and EF	Sz-S significantly lower IQ, spatial working memory, verbal memory, attention, and EF scores compared to Comp and Sz significantly worse than Comp group on all measures	IQ: *d* =-0.99 Working memory: spatial back span, *d*=-0.86 Verbal memory: letter number, *d* =-0.88 Attention: *d* =-0.69 EF: letter fluency, *d* =-0.72, category fluency, *d* =-0.87
Fis *et al.*, (2008)	30 Sz-O and 30 Comp	8-15 years	IQ and EF	Sz-O exhibited significantly lower IQ and poorer EF than Comp group	IQ: verbal IQ, *d* =-0.72; performance IQ, *d* =-1.19; full scale IQ, *d*=-1.04 EF[15]: TMT-A, *d* =-0.53; TMT-B, *d* =-0.81; colour form test, *d* =-0.87; progressive figure test, *d* =-0.71
Bhojraj *et al.*, (2009)	60 Sz-R and 42 Comp	9-25 years	EF	Sz-R significantly impaired on verbal fluency task (letter not category fluency) compared to Comp group	EF: Letter fluency, *d* =-0.45

[15] TMT-A= Trial Making Test-A; and TMT-B= Trial Making Test-B

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Chen *et al.*, (2009)	65 Sz-S, 56 Sz, 77 Comp, and 80 Comp-S	Sz-S (22 yrs) / Sz (22 yrs) / Comp (20yrs) / Comp-S (19 yrs)	Working memory, memory/learning, attention, and EF	Sz-S significantly worse than Comp-S on working memory, memory/learning, and EF domains	Working memory: *d* =-0.21 Memory/learning: *d* =-0.45 EF: *d* =-0.20
Maziade *et al.*, (2008)	22 Sz-O and 45 Comp	Sz-O (17 yrs) / Comp (17 yrs)	IQ, verbal memory/learning/ visual memory, attention, spatial working memory, and EF	Sz-O significantly lower IQ and worse performance on verbal memory/learning, visual memory, and EF compared to Comp	IQ: *d* =-1.56 Verbal memory/learning: recall, *d* =-0.57; delay recall, *d* =-0.86 Visual memory: recall, *d* =-0.92; delay recall, *d* =-0.86 EF[16]: letter fluency, *d* =-0.72; TOL, *d* =-0.58
O'Connor *et al.*, (2009)	97 Sz-R and 25 Comp	Sz-R (25 yrs) / Comp (26.yrs)	Working memory, spatial working memory, and EF	Sz-R impaired on working memory and EF measures (planning speed) compared to Comp	Working memory: *d* =-0.46 EF: *d* =- 0.48

[16] TOL= Tower of London Test

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Keshavan *et al.*, (2010)	145 Sz-R and 109 Comp	10-25 yrs	IQ, psychomotor speed, attention, spatial working memory, and EF	Sz-R exhibited significantly lower IQ, poorer psychomotor speed, attention, and EF (verbal fluency only) compared to Comp	IQ: insufficient data to calculate effect size Psychomotor speed: *d* =-0.73 Attention: *d* =-0.46 EF: Verbal fluency, *d* =-0.63
Ozan *et al.*, (2010)	30 Sz-O and 37 Comp	Sc-O (12 yrs) / Comp (12 yrs)	Working memory, verbal memory/learning, attention, and EF	Sz-O significantly worse on working memory, verbal memory, and EF domains	Working memory: *d* =-0.87 Verbal memory: total, *d* =-0.68; delay recall, *d* =-0.67: EF[17]: TMT-A *d* =-0.97; TMT-B *d* =-0.40; Stroop *d* =-0.59; WCST total, *d* =-0.53; WCST errors, *d* =-0.53

[17] TMT-A= Trial Making Test A; TMT-B= Trial Making Test B; and WCST= Wisconsin Card Sorting Test

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
de la Serna *et al.*, (2011)	30 Sz-O, 26 Sz-S, and 33 Comp	Sz-O (10 yrs) / Sz-S (12 yrs) / Comp (11 yrs)	IQ, working memory, verbal memory/learning, visual memory, perceptual organisation, and EF	Both Sz-O and Sz-S groups impaired on IQ, verbal memory, and perceptual organisation compared to Comp but Sz-O also impaired on visual memory relative to Comp and working memory compared to Sz-S.	IQ: **Sz-O** *d* =-1.5, **Sz-S** *d*=-0.98 Verbal Memory: immediate recall, **Sz-O** *d* =-0.71, **Sz-S** *d*=-0.94; delayed recall, **Sz-O** *d* =-0.94, **Sz-S** d=-0.97 Visual Memory: **Sz-O** *d* =-1.19 Perceptual Organisation: **Sz-O** copy figure *d* =-1.33; delay recall figure**,** **Sz-O** *d* =-1.21, **Sz-S** *d*=-0.79
Diwadkar *et al.*, (2011)	36 Sc-O and 41 Comp	Sz-O (14 yrs) / Comp (14 yrs)	Working memory and attention	Sc-O significantly poorer on working memory but not attention compared to Comp	Insufficient data to calculate effect sizes
Forsyth *et al.*, (2012)	373 Sz-O and 1070 Comp	15-16 yrs	Scholastic achievement (9th grade Finnish overall school mark)	Sz-O exhibited lower overall school marks than Comp group	Insufficient data to calculate effect sizes
Jundong *et al.*, (2012)	3654 Sz-O and 1,439 215 offspring of a parent without schizophrenia	15 years	Scholastic achievement (9th grade Swedish overall school mark)	Sz-O significantly poorer than offspring of individuals without schizophrenia	Insufficient data to calculate effect sizes

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Scala *et al*., (2013)	41 Sz-S/O and 54 Comp	Sz-S/O (19 yrs) / Comp (17 yrs)	Verbal and visual memory	Sz-S/O performed significantly more poorly than Comp group on verbal recall and visual memory organisation	Verbal recall: *d* =-0.51 Visual memory organisation: *d* =-0.58
Longitudinal studies of repeated cognitive assessments among individuals with a positive family history					
Worland *et al.*, (1982)	10 Sz-O and 75 Comp	Baseline: 5 yrs / Follow-up: 16 yrs	IQ	No significant differences between groups at baseline but Sz-O exhibited a significant decline in verbal IQ relative to Comp group at follow-up	Insufficient data to calculate effect sizes
Goodman, (1987)	71 Sz-O and 38 Comp	Birth-5 yrs (at baseline assessment)	IQ (assessed 3 times and 1 yr intervals)	SZ-O exhibited significantly lower IQ compared to Comp group at baseline assessment only	IQ: Baseline assessment *d* = -0.55

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Cosway *et al*., (2000)	78 Sz-R and 22 Comp	16-25 yrs (at baseline assessment)	IQ, processing speed, memory/learning, verbal ability/language, mental control/encoding and EF. Assessment repeated 18-24 months later	Sz-R significantly lower IQ, processing speed, verbal memory and EF relative to Comp. No significant group x time interaction observed.	**Baseline**: IQ: *d* =-0.56 Processing speed: *d* =-0.45 Verbal memory: immediate recall, *d* =-0.53; delay recall, *d* =-0.56 EF: Verbal fluency (semantic), *d* =-0.38 **Follow-up**: IQ: *d* =-0.46 Processing speed: *d* =-0.63 Verbal memory: immediate recall, *d* =-0.38; delay recall, *d* =-0.61 EF[18]: Verbal fluency (semantic), *d* =-0.50 Not able to calculate effect sizes for HCST errors at either assessment

[18] HCST= Hayling Sentence Completion Task

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Ross *et al.*, (2008)	25 Sz-O and 82 Comp	Sz-O 9 yrs at baseline / Sz-O 12yrs at follow-up / Comp 11 yrs and only tested once	Working memory and inhibition (assessments repeated in Sz-O group approximately 2.6 yrs later)	Significant group differences at baseline but borderline at follow-up assessment. No group x time interaction observed	**Baseline** Inhibition: *d* =-0.46 Verbal working memory: *d* =-0.50 **Follow-up** Inhibition: *d* =-0.53 Verbal working memory: *d* =-0.42
Bhojrai *et al.*, (2010)[19]	24 Sz-S/O and 28 Comp	Sz-S/O (14 yrs) / Comp group (15yrs)	Attention and EF (assessments repeated at 1 yr and 2 yr later)	Sz-S/O significantly worse than Comp on attention and EF. Over time, Comp significantly improved while Sz-S/O performance remained the same for EF.	**Baseline** Attention: *d* =-0.54 EF: *d* =-0.21 **1 yr follow-up** Attention: *d* = -0.46 EF: *d* =-0.90 **2 yr follow-up** Attention: *d* =-0.62 EF:*d* =-0.1.2
Sanchez-Torres *et al.*, (2012)	34 Sz-S, 34 Sz and 13 Comp group	Sz-S (27 yrs) / Sz (28 yrs) / Comp (30 yrs)	EF assessments repeated 10 yrs later	No differences observed between Sz-S and Comp group with Sz group performing significantly worse overall	

[19] Effect size calculated from F statistic

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Cross-sectional studies of youth meeting Ultra High-Risk criteria					
Gschwandtner *et al.*, (2003)	32 Ultra-High-Risk (UHR) and 32 Comp	UHR (26 yrs)/ comp (25 yrs)	Working memory, EF, and attention	UHR group significantly poorer performance on working memory, EF and attention relative to Comp	Working memory: *d*=-1.04 EF[20]: WCST, *d*=-0.6; TOH, *d*=0.79 Attention: *d*=-0.85
Hawkins *et al.*, (2004)	36 UHR (SIPS/SOPS)	UHR (19 yrs)	IQ, attention, working memory, processing speed, spatial perception, memory, and EF	Compared to age and sex normative data, UHR group were significantly impaired on attention, processing speed, working memory, verbal memory, and EF	Insufficient data to calculate effect sizes
Bartok *et al.*, (2005)	11 UHR individuals	UHR (25 yrs)	Memory/Learning, EF, and attention	Compared to age and gender matched normative data, UHR individuals performed significantly more poorly on memory (spatial)/learning and attention measures	Insufficient data to calculate effect sizes

[20] TOH= Tower of Hanoi

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Pukrop *et al.*, (2006)	128 UHR, 86 first-episode psychosis patients (FEP), 88 (Sz), and 179 Comp group. UHR group split into "early" prodromal phase (UHR-E, n=38) and "late" prodromal phase (UHR-L, n=90)	UHR (24 yrs) / FE (29 yrs) / Sz (31 yrs) / Comp (29 yrs).	Attention, memory/learning, and EF	UHR group exhibited significantly lower performance on verbal memory and EF measures relative to Comp (see effect sizes) and UHR-E were impaired on verbal memory whilst UHR-L were impaired on attention, verbal memory and EF compared to Comp Sz and FEP significantly worse overall	Verbal memory: *d*=-0.58 EF: *d*=-0.96
Smith *et al.*, (2006)	8 UHR and 10 Comp	UHR (16 yrs) / Comp (16 yrs)	IQ, spatial working memory	UHR group significantly impaired on spatial working memory but not IQ relative to Comp	Spatial working memory: error distance, *d*= -1.2; errors, *d*= -1.9
Niendam *et al.*, (2006)	45 UHR	UHR (17 yrs)	Processing speed, reasoning/problem solving, memory/learning, and verbal working memory	UHR group displayed poorer performance on processing speed and verbal memory/learning measures compared to age and gender matched normative data	Insufficient data to calculate effect sizes
Broome *et al.*, (2007)	35 UHR and 23 Comp	UHR (24 yrs) and Comp (24 yrs)	Working memory	No differences between groups on working memory task with a 'easy' load although significant differences reported at increased load	Working memory: intermediate load, *d* =-1.06; Hard load, *d* =-0.75

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Pfluger *et al.*, (2007)	60 UHR and 51 Comp	UHR (27 yrs) / Comp (23 yrs)	IQ, attention, working memory, and EF	UHR groups performed significantly more poorly on all cognitive domains (except nonverbal IQ) compared to Comp	Insufficient data to calculate effect sizes.
Silverstein *et al.*, (2006)	70 UHR, 54 FEP, and 24 Comp	UHR (17 yrs) / FEP (18 yrs) / Comp (20 yrs)	Perceptual organisation	No significant differences between groups	
Simon *et al.*, (2007)	69 UHR, 24 individuals reporting basic symptoms (UHR-BS), 43 FEP patients, and 49 Comp	UHR (20 yrs)/ UHR-BS (21 yrs) / FE (22 yrs), and Comp (21 yrs).	IQ, verbal memory/learning, attention, processing speed, and EF	UHR group demonstrated intermediate levels between FE and UHR-BS groups on all domains. Only UHR group exhibited significantly poorer performance on verbal working memory compared to Comp (see effect size)	Verbal working memory: d =-0.43
Ozgurdal *et al.*, (2009)	54 UHR and 37 FEP	UHR (24 yrs) / FEP (28 yrs)	IQ, attention, verbal memory, and EF	FEP performed significantly worse than UHR group on measures of nonverbal IQ, attention, and EF.	Insufficient data to calculate effect sizes.
Lindgren.*et al.*, (2010)	62 UHR, 112 Comp-HS, and 72 Comp	UHR (16 yrs) / Comp-HS (16 yrs) / Comp (16 yrs)	Reasoning/ problem-solving, memory, working memory, visuomotor speed, attention, and EF	UHR significantly worse than Comp-HS on spatial working memory, verbal fluency (semantic), and visuomotor speed	Spatial working memory: d =-0.65 Verbal fluency: d =-0.39 Visuomotor speed: d =-0.48

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Carrion *et al*, (2011)[21]	127 UHR and 80 Comp	UHR (16 yrs) / Comp (16 yrs)	Verbal memory, processing speed, working memory, visuospatial processing, attention, language, and EF	UHR impaired on all cognitive domains relative to Comp	Verbal memory: *d* =-0.86 Processing speed: *d* =-0.74 Working Memory: *d* = -0.54 Visuospatial processing: *d* =-0.40 Attention: *d* =-0.32 Language: *d* =-0.32 EF: *d* = -0.44
Frommann *et al.*, (2011)	116 UHR-E, 89 UHR-L, and 87 Comp	UHR-E (25 yrs) / UHR-L (25 yrs) / Comp (25 yrs)	Memory/learning, processing speed, attention, working memory, and EF	UHR-L significantly impaired on all domains compared to Comp whilst UHR-E impaired only on verbal learning, processing speed, and EF	Insufficient data to calculate effect sizes
Kim *et al.*, (2011)	27 UHR, 25 FEP, and 33 Comp	UHR (19 yrs) / FEP (21 yrs) / Comp (19 yrs)	IQ, attention/working memory, memory/learning, and EF	UHR performed significantly worse on measures of verbal memory, attention/working memory, and EF compared to Comp and FEP significantly impaired on all domains compared to Comp	Verbal memory: *d* =-0.71 Attention/working memory: *d* =-0.70 EF: *d* =-0.86

[21] Effect size converted from Cohen's *f* statistics to a Cohen's *d*

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Longitudinal studies of repeated cognitive assessment among youth meeting Ultra High-Risk criteria					
Keefe *et al.*, (2006)	37 UHR, 59 FEP and 47 Comp	UHR (20 yrs) / FEP (24 yrs) / Comp (24 yrs)	Verbal memory/learning, verbal fluency, working memory, attention, and processing speed (assessments repeated at 6 and 12 months)	UHR significantly worse over time on verbal fluency and processing speed relative to Comp and FEP significantly poorer on all domains	Insufficient data to calculate effect sizes
Niendman *et al.*, (2007)	35 UHR (SIPS/SOPS)	17 yrs (assessments repeated 8 months later)	Processing speed, Reasoning/problem solving, verbal memory/learning, visual memory/learning, and verbal working memory	**Baseline**: UHR impaired relative to normative data on processing speed and verbal memory/learning **Follow-up**: improvement on all domains except reasoning/problem solving and verbal working memory	Insufficient data to calculate effect sizes
Fusar-Poli *et al.*, (2010)	15 UHR and 15 Comp	UHR (24 yrs) / and Comp (25 yrs) (assessment repeated 12 months later)	Spatial working memory	No differences between groups at baseline or follow-up assessment	

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Jahshan *et al.*, (2010)	48 UHR, 20 FEP and 29 Comp	UHR (18 yrs) / FEP (19 yrs) / Comp (19 yrs) (assessments repeated 6 months later)	IQ, working memory, verbal learning, processing speed, and EF	UHR worse than Comp on working memory (see effect sizes) but UHR showed a small improvement in IQ over time. FEP significantly worse than UHR on all domains	**Baseline**: Working memory: letter-number, *d* =-0.57; spatial span backwards, *d* =-0.47 **Follow-up:** Working memory: letter-number, *d* =-0.36; spatial span backwards, *d* =-0.49
Barbato *et al.*, (2013)	71 UHR	19 yrs	IQ, verbal memory, verbal working memory, spatial working memory, attention, and EF	Improvements on all domains except verbal memory and EF (verbal fluency only)	Insufficient data to calculate effect sizes
Woodberry *et al.*, (2013)	53 UHR and 32 Comp	UHR (16 yrs) / Comp (16 yrs) (assessments repeated 12 months later)	IQ, attention, verbal memory/learning, and EF (assessments repeated 12 months later)	Improvement in IQ among UHR and Comp at 12 months compared to baseline but verbal memory and EF lower than predicted levels at follow-up in UHR	Insufficient data to calculate effect sizes

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Studies comparing individuals with a positive family history and youth meeting Ultra High-Risk criteria					
Myles-Worsley *et al.*, (2007)[22]	98 Sz-R, 113 UHR, and 99 Comp	14-19 yrs	Perceptual organisation, processing speed, verbal/visual memory, working memory, and attention	Relative to Comp group, Sz-R significantly worse on verbal memory, verbal working memory, and attention. In contrast, UHR impaired on perceptual organisation and spatial working memory	**Sz-R Vs Comp group:** Verbal memory: immediate, *d* =-0.67 Verbal working memory: *d* =-0.37 Attention: numbers, *d* =-0.59; shapes, *d* =-0.37 **UHR Vs Comp group:** insufficient data calculate effect sizes
Seidman *et al.*, (2010)	304 UHR, 52 Sz-R, and 193 Comp UHR group: UHR who did not transition to psychosis (UHR-NP, n=169) and UHR cases who did transition to psychosis (UHR-P, n=73)	Sz-R (18 yrs) / UHR (18 yrs) / Comp (18 yrs)	IQ, verbal ability, perceptual organisation, attention, processing speed, verbal memory/learning, and EF	**Sz-R Vs Comp**: Impaired on processing speed and verbal ability **UHR Vs Comp**: Impaired on processing speed, verbal memory, attention, and EF (verbal fluency) UHR-P had significantly poorer verbal ability than UHR-NP and verbal memory was a significant predictor of time to transition.	Insufficient data to calculate effect size

[22] Effect size taken for Sz-R taken from Agnes-Blais and Seidman (2012)

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Mukkala *et al.*, (2011)	62 Sz-O, 20 UHR, 13 Sz, and 69 Comp	Sz-O (22 yrs) / UHR (22 yrs) / Sz (23 yrs) / Comp group (22 yrs)	IQ, verbal memory/learning, working memory/attention, and EF	Sz-O and UHR groups did not differ significantly from Comp	
Studies of children/adolescents experiencing psychotic like-experiences					
Horwood *et al.*, (2008)	6,455 members of British birth cohort (Avon Longitudinal Study of Parents and Children: ALSPAC)	IQ assessment at 8 yrs and PLEs assessed in clinical interview at 12 yrs	IQ	Children with a below average IQ had an increased risk of reported definite and suspected PLEs	Insufficient data calculate effect sizes
Polanczyk *et al.*, (2010)	2232 children from the Environmental Risk (E-Risk) Longitudinal Twin Study PLEs present n=125/ PLEs not present n=2002	5 yrs	IQ and EF	Children with PLEs exhibited significantly lower IQ relative to children without PLEs.	IQ: *d* =-0.50
Blanchard *et al.*, (2010)	37 adolescents recruited from a community-based PLE screening programme in Ireland (adolescents with PLEs n=17/ adolescents without PLEs n=20)	11-13 yrs	Memory, language, abstract reasoning, attention, processing speed, and scholastic achievement/IQ	Children reporting PLEs were significantly worse on measures of receptive language and processing speed than children without PLEs	Receptive language: *d*=-1.06; Processing speed: *d*=-0.62

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Bartels-Velthuis *et al.*, (2011)	Baseline study of 694 Danish children aged 7-8 yrs 5 years later 337 available for follow-up (persistent auditory hallucination group n=40/ no auditory hallucination at either group assessment n=125)	12/13 yrs	Scholastic Achievement	Children with persistent auditory hallucinations had significantly lower end of primary school marks than children who had never reported these experiences at either assessment phase	Scholastic Achievement: *d*=-0.64
Kelleher *et al.*, (2012)	165 adolescents recruited from a community-based screening programme in Ireland (adolescents with PLEs (n=42/adolescents without PLEs n=123)	11-13 yrs	Processing speed, verbal learning/memory, nonverbal working memory, verbal working memory, reasoning /problem solving, visual learning, and attention/vigilance and Scholastic Achievement/IQ	Children reporting PLEs were significantly worse on all measures of processing speed and nonverbal working memory than children without PLEs	Processing speed: TMT-A[23] *d*=-0.23; TMT-B [12] *d*=-0.57; Digit Symbol Coding Task, *d*=-0.52. Nonverbal working memory: *d*=-0.17

[23] TMT-A= Trial Making Test-A; and TMT-B= Trial Making Test-B

Study	Sample	Mean Age	Domain	Results	Effect size (Cohens *d*)
Kim *et al.,* (2012)	Community-based sample of 2159 students from Korea High-PLE n=87/Low-PLE n=2072)	High-PLE (17 yrs), Low-PLE (17 yrs)	Attention	High-PLE group made significantly more omission and commission errors in divided attention task but not sustained attention task compared to Low-PLE group	Divided attention: Omission errors, *d*=-0.31; commission errors, *d*=-0.22
Hameed *et al.,* (2013)	6790 members of ALSPAC cohort	7 and 9 years	Scholastic Achievement/Literacy skills	Consistently low and declining patterns of scholastic achievement/literacy skills were associated with suspected and definite PLEs at 12 years	Insufficient data to calculate effect sizes
Niarchou *et al.,* (2013)	6121 members of ALSPAC cohort	8,10 and 11 years	Attention / Vigilance, reasoning and problem solving, and processing speed (8 and 11 years), and working memory (8 and 10 years)	Poorer performance in domains of processing speed, attention, working memory, and an improvement in processing speed between 8 and 11 years associated with higher risk of PLEs at 12 years	Insufficient data to calculate effect sizes

Chapter 6 Childhood cognitive impairment across aetiologies for schizophrenia

6.1 Aims of chapter

The present study examined neurocognitive impairments in children defined as being at-risk for schizophrenia either by the presence of affected relatives or by the presence of multiple antecedents of the disorder. The aims were to determine whether impairments differed depending on the definition of risk and/or on the degree of relatedness to an affected individual. Therefore, we compared performance on a broad array of neurocognitive tests among four groups of children aged 9-12 years, namely: (1) ASz; (2) children with at least one first-degree or two second-degree affected relative (i.e., high family loading: FHx^{H}); (3) one affected second-degree relative (i.e., lower family loading: FHx^{L}); and (4) typically-developing (TD) children. We anticipated that all three high-risk groups of children, ASz, FHx^{H}, and FHx^{L}, would display poorer neurocognitive performance in IQ, scholastic achievement, memory, and executive function than TD children, and that the specific impairments would differ across the risk groups (Myles-Worsley *et al.*, 2007, Seidman *et al.*, 2010). We also expected that children with a higher degree of family loading for schizophrenia (FHx^{H}) would exhibit more severe neurocognitive impairments than those in whom the degree of family loading was presumed to be lower (FHx^{L}). The study also determined the extent to which IQ explains differences in neurocognitive performance among children defined as ASz, FHx^{H}, and FHx^{L}.

6.2 Method

6.2.1 Sample

One hundred and four children aged 9-12 years were recruited via school screening procedures or as relatives of patients receiving treatment within the South London and

Maudsley National Health Service Foundation Trust described in Chapter Two and Three of the thesis.

Children presenting antecedents of schizophrenia (ASz) met three criteria: (1) a child-reported "certainly-true" response on at least one of nine psychotic like-experiences (PLE) items assessing hallucination- and delusion-like experiences (Laurens *et al.*, 2012); (2) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (Goodman, 2001); and (3) a caregiver-report of a motor and/or speech delay and/or abnormality (Laurens *et al.*, 2007). In contrast, TD children were defined as those who presented none of the three ASz criteria nor had a first-, second-, or third-degree relative with a schizophrenia spectrum disorder as confirmed using the Family Interview for Genetic Studies with the child's primary caregiver (FIGS: Maxwell, 1992).

FHx children had at least one second-degree relative with schizophrenia (n=25) or schizoaffective disorder (n=2), confirmed by the FIGS (Maxwell, 1992) conducted with the child's caregiver. Initially, a genetic liability score was computed based on the degree of relatedness and the number of affected relatives (Campbell *et al.*, 2010). With the exception of two children with two affected second-degree family members, the results showed a bimodal distribution distinguishing FHx children with and without a first-degree affected relative. A previous study detected no differences in neurocognitive impairment between adolescents with an affected parent and those with two affected second-degree relatives with schizophrenia (Myles-Worsley *et al.*, 2007). Consequently, FHx children were divided into two groups. The high familial loading for schizophrenia (FHx^{H}) group was defined to include children with one first-degree and one second-degree relative (n=4), one first-degree relative only (n=7), or two second-

degree relatives (n=2) with schizophrenia or schizoaffective disorder. The low familial-loading group (FHx^{L}) included children with only one second-degree relative with the disorder.

None had ever experienced a psychotic episode or taken anti-psychotic medication, nor presented a neurological disorder (e.g., epilepsy), learning difficulties (IQ < 70), or had a diagnosis of autism or Asperger's disorder.

The final sample comprised four groups: 32 ASz, 13 FHx^{H}, 14 FHx^{L}, and 45 TD children. One FHx^{H} child and four FHx^{L} children also met ASz criteria, but were retained in their respective FHx groups. Table 11 presents demographic comparisons of the four groups. Groups were similar as to age at the time of neurocognitive assessment, handedness, and proportions male, but differed as to self-ascribed ethnicity, and parents' occupational status.

Table 11. Demographic characteristics for ASz, FHx^H, FHx^L, and TD children age 9 to 12 years

	ASz (n=32)		FHx^H (n=13)		FHx^L (n=14)		TD (n=45)		Statistics
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Sex (Male)	22	(63)	7	(69)	5	(54)	21	(48)	X^2=5.6, (df=3), p=0.1
Laterality									
Right-hand dominance	25	(77)	12	(92)	12	(86)	39	(87)	*Fisher's Exact Tes*t, p=0.7
Mixed- or left-hand dominance	7	(23)	1	(8)	2	(14)	6	(13)	
Ethnicity[a]									
White	15	(47)	2	(15)	3	(21)	33	(73)	
Black African and African-Caribbean	9	(28)	7	(54)	3	(43)	7	(16)	*Fisher's Exact Test*, p=0.001
Other	8	(25)	4	(31)	5	(36)	5	(11)	
Social Class based on parental occupation[b]									
Professional, managerial and technical occupations	17	(53)	5	(38)	10	(71)	39	(87)	*Fisher's Exact Test*, p=0.001
All skilled/unskilled manual occupations	15	(47)	8	(62)	4	(29)	6	(13)	
	Mean	**sd**	**Mean**	**sd**	**Mean**	**sd**	**Mean**	**sd**	
Age on day of assessment	10y,11m	12m	11y, 3m	13m	10y, 7m	13m	11y, 0m	10m	F(3,100)=1.1, p=0.4

Notes: y = years, m = months; a"Black African and Black African-Caribbean" included children of mixed white-black African/African-Caribbean ethnicity. "Other" included children predominantly of other mixed ethnicities. b Social class based on Occupation (Office of Population Censuses and Surveys, 1980).

6.2.2 Procedure

Eligible children and their primary caregivers were invited to participate in a research study in which children completed a battery of neurocognitive assessments in addition to biological and psychosocial measures. Caregivers provided information on parental occupational status using UK Standard Occupational Classification 2000 (Statistics., 2001).

Ethical approval of the study was obtained from the Joint South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry Research Ethics Committee. Children provided written assent and caregivers provided written consent for participation in the study.

6.2.3 Neurocognitive assessments

A brief description of each neurocognitive measure comprising the test battery is provided in Table 12.

Each neurocognitive subtest provided standardised scores based on manual-reported, age-adjusted normative data; only the WIAT-II UK provided norms for samples of children from the UK. A scholastic achievement domain score was created by adding standardised scores for each participant on word reading, numerical operations, and spelling subtests and then dividing the total score by number of subtests. Scores for each subtest were converted into standardised z-scores based on TD group (risk group mean minus TD mean, divided by the TD standard deviation), so that the TD group had a mean of 0 and a standard deviation of 1.

Table 12. Details of neurocognitive assessments

Cognitive measure	Test Description
Intelligence	
Verbal Comprehension	
- Vocabulary	Define orally and visually presented words
- Similarities	Identify similarities between pairs of words
Perceptual Reasoning	
- Block Design	Replicate geometric patterns using two-coloured cubes within a specified time limit
- Matrix Reasoning	Choose one shape from five to complete a pattern
Scholastic Achievement	
- Word Reading	Read aloud a word list
- Numerical Operations	Complete mathematical problems
- Spelling	Write verbally presented words
Memory	
Verbal Memory	
- Story Memory	Immediate recall of details from two short stories read aloud
- Verbal Learning	Immediate free recall of word list (four trials)
Visual Memory	
- Design Memory	Immediate recall of five geometric designs
- Picture Memory	Identify differences between four similar pairs of pictures.
- Verbal Working Memory	Immediate recall of word lists by animal and non-animal categories
Executive Functioning	
Verbal Fluency	
- Letter Fluency	Generate words beginning with F, A, and S in 60 seconds
- Category Fluency	Generate animals and boys' names in 60 seconds
- Category Accuracy	Alternatively generate words from fruits and furniture categories in 60 seconds
Colour Word interference	
- Inhibition	Name ink colour of colour words printed in different colour ink (Stroop, 1935).
- Inhibition/Switching	As for Inhibition subtest; or, reading colour word (ignore printed ink colour)
Towers Test	
- Towers Test Achievement score	Build towers using one to five pegs in the fewest possible number of moves

6.2.4 Statistical analyses

Univariate ANOVA and chi-square tests were used to compare groups on demographic variables. The distributions of raw scores and standardised z-scores were assessed for normality and outliers. Scores for the scholastic achievement domain of two TD children diagnosed with dyslexia were excluded, as was the perceptual reasoning score of one ASz child with a diagnosis of dyspraxia. To compare scores on the neurocognitive tests of the four groups, analysis of covariance (ANCOVA) tests were conducted adjusting for ethnicity and parents' occupational status, with post-hoc Bonferroni-Hochberg correction applied (Hochberg, 1988). The size of the group differences is expressed as Cohen's *d* effect sizes (Cohen, 1988). To explore the role of general intellectual ability on specific domains of neurocognitive performance, ANCOVA analyses were repeated with the inclusion of full-scale IQ as an additional covariate.

6.3 Results

6.3.1 Group comparisons of neurocognitive performance

Standardised z-scores calculated for each test and for each risk group relative to the TD group are presented in Figures 6 and 7. FHx^{H} children exhibited poorer neurocognitive performance on all measures except visual memory, while ASz children performed at an intermediate level relative to the FHx^{H} and FHx^{L} groups. Neurocognitive performance of FHx^{L} children in all domains except visual memory fell between that of ASz and TD groups.

Tables 13 and 14 present mean scores for performance of each group on the neurocognitive tests, the results of ANCOVAs adjusting for ethnicity and parents' occupation, and the significant post-hoc group comparisons. Significant overall group differences were obtained for full-scale IQ, verbal comprehension, scholastic

achievement, verbal memory, verbal working memory, EF- category accuracy, and EF – inhibition/switching.

Table 13. Comparisons of general intelligence and scholastic achievement of ASz, $FHx^{H,}$ $FHx^{L,}$ and TD children

Subtest variable	ASz (n=32)	FHx^{H} (n=13)	FHx^{L} (n=14)	TD (n=45)	ANCOVA adjusted for ethnicity and parents' occupation		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F (df); p	Significant post-hoc tests	Cohen's *d*
General Intelligence							
Full scale IQ	103.1 (11.8)	92.8 (13.7)	107.4 (14.3)	114.9 (15.0)	4.2 (3,98); 0.008	FHx^{H} < TD	*d*=1.1
Verbal Comprehension	101.9 (12.3)	93.3 (10.8)	109.1 (14.2)	113.9 (14.6)	4.7 (3,98); 0.004	FHx^{H} < TD ASz<TD	*d*=1.3 *d*=0.9
Perceptual Reasoning	102.6 (13.5)	93.8 (17.0)	103.5 (12.7)	113.2 (15.4)	2.6 (3.97); 0.06	FHx^{H} < TD	*d*=1.2
Scholastic Achievement	94.9 (12.0)	89.6 (12.3)	102.7 (8.3)	104.4 (11.0)	4.5 (3,93); 0.006	FHx^{H} < TD ASz < TD FHx^{H} < FHx^{L}	*d*=1.3 *d*=0.8 *d*=1.3

Notes: Information on scholastic achievement was not available for 2 ASz participants. ANCOVA statistics include F statistic, degrees-of-freedom and p-value, and are adjusted for ethnicity and parents' occupation. Only post-hoc tests that were significant after Bonferroni-Hochberg corrections for multiple testing are reported.

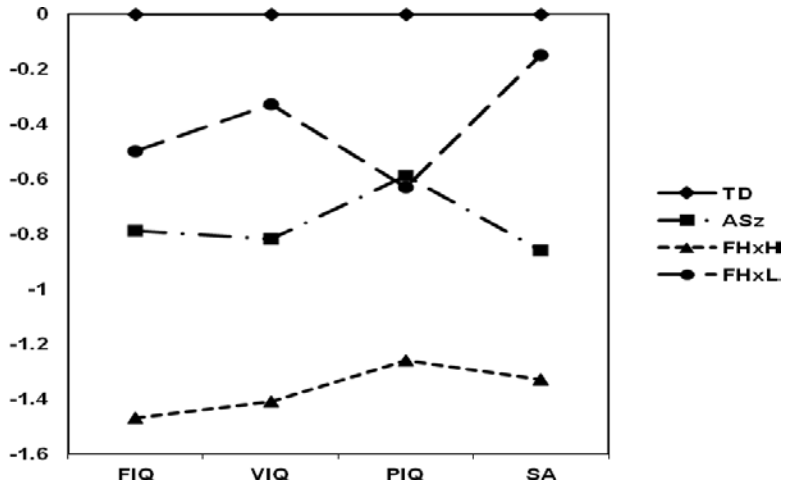
Table 14. Comparisons of memory and executive functioning of ASz, FHx^H, FHx^L, and TD children

Subtest variable	ASz (n=32)	FHx^H (n=13)	FHx^L (n=14)	TD (n=45)	ANCOVA adjusted for ethnicity and parents' occupation		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F (df); p	Significant post-hoc tests	Cohen's *d*
Memory							
Verbal Memory	21.7 (4.6)	17.2 (5.1)	21.6 (3.6)	23.9 (4.8)	3.1 (3, 97); 0.03	FHx^H < TD	*d*=0.9
Visual Memory	16.7 (4.7)	18.8 (5.0)	15.5 (5.6)	18.8 (3.5)	2.5 (3, 97); 0.06		
Verbal Working Memory	9.7 (2.2)	9.1 (2.4)	10.0 (2.0)	11.5 (2.5)	3.8 (3, 96); 0.01	ASz < TD FHx^H < TD	*d*=0.7 *d*=1.0
Executive Functioning							
Verbal Fluency							
Letter Fluency	10.5 (3.2)	10.2 (2.4)	11.5 (3.6)	11.5 (2.6)	1.5 (3, 97); 0.22		
Category Fluency	12.2 (2.9)	11.4 (2.2)	12.0 (3.4)	12.8 (2.8)	0.1 (3, 96); 0.93		
Category Accuracy	10.2 (2.9)	7.2 (3.4)	10.4 (1.5)	11.2 (2.8)	4.4 (3, 97); 0.01	FHx^H < TD FHx^H < TD FHx^H < FHx^L	*d*=1.4 *d*=1.0 *d*=1.3
Colour Word Interference							
Inhibition	10.7 (2.3)	9.1 (3.5)	10.6 (1.7)	11.7 (2.3)	1.5 (3, 96); 0.22		
Inhibition/Switching	10.5 (2.8)	8.8 (2.5)	11.1 (2.2)	11.2 (2.0)	2.9 (3, 96); 0.04	FHx^H < TD	*d*=1.2
Towers Test							
Towers Test Achievement Score	10.6 (2.4)	10.3 (2.3)	10.8 (1.8)	11.2 (2.6)	0.2 (3, 95); 0.90		

Notes: Data were missing for memory, verbal working memory, and executive functioning for 1 ASz participant, category fluency for 1 FHx^H participant, inhibition/switching for 1 TD participant and achievement score on the Towers test for 1 ASz and TD participant. Scores for inhibition from 1 FHx^H participant were excluded as an outlier. ANCOVA statistics include F statistic, degrees-of-freedom, and p-value. Only post-hoc tests that were significant after Bonferroni-Hochberg corrections for multiple testing are reported.

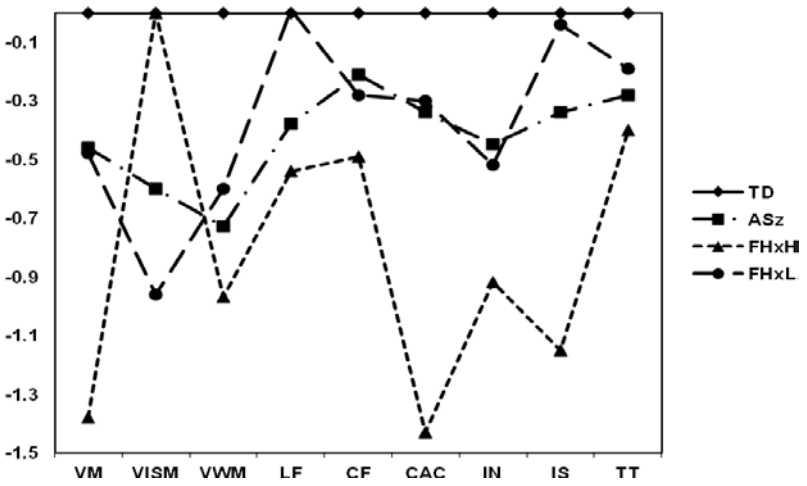
Post-hoc group comparisons with corrections for multiple testing indicated that ASz children obtained lower verbal comprehension scores and poorer scholastic achievement and verbal working memory than TD children. FHx^{H} children performed significantly more poorly than the TD children on full-scale IQ, verbal comprehension, perceptual reasoning, scholastic achievement, verbal memory, verbal working memory, EF-category accuracy, and EF-inhibition/switching domains, with large effect size differences. FHx^{H} children also displayed poorer performance on EF-category accuracy relative to both FHx^{L} and ASz children, and on scholastic achievement compared to FHx^{L} children. The performance of the FHx^{L} children did not differ significantly from that of the TD children on any test.

Figure 6. Group z-scores of intelligence and scholastic achievement scores standardised to the typically developing group



Notes: FIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; SA = scholastic achievement domain score; TD = typically developing children without antecedents or family history of schizophrenia; ASz = children presenting with multiple antecedents of schizophrenia; FHxH = children with high familial loading for schizophrenia; and FHxL = children with low familial loading.

Figure 7. Group z-scores of memory and executive functioning scores standardised to the typically developing group mean.



Notes: VM = verbal memory; VISM = visual memory; VWM = verbal working memory; LF = verbal fluency: letter fluency; CF = verbal fluency: category fluency; CAC = verbal fluency: category fluency accuracy; IN = colour word interference: inhibition; IS = colour word interference: inhibition/switching; TT, towers test achievement score; TD = typically developing children without antecedents or family history of schizophrenia; ASz = children presenting with multiple antecedents of schizophrenia; FHx^{H} = children with high familial loading for schizophrenia; and FHx^{L} = children with low familial loading.

6.3.2 Does IQ explain group differences in neurocognitive performance?

When full-scale IQ was entered as an additional covariate in ANCOVA models, overall group differences on neurocognitive measures were attenuated, such that only scores for EF- inhibition/switching [F(3, 95) =2.7, p=0.05] and visual memory [F(3, 96) =2.9, p=0.04] significantly differed across the four groups. Post-hoc group comparisons, with corrections for multiple testing applied, indicated that FHx^{L} children obtained significantly lower visual memory scores than FHx^{H} (p=0.01). On the EF-inhibition/switching subtest, FHx^{H} performed significantly more poorly compared to the FHx^{L} (p=0.02) and TD groups (p=0.007).

6.4 Discussion

The present study examined neurocognitive functioning of three groups of children aged 9-12 years at-risk for schizophrenia, relative to TD peers. Compared to TD children, FHx^{H} children exhibited lower full scale, verbal comprehension and perceptual reasoning scores, and poorer scholastic achievement, verbal memory, verbal working memory, category switching and inhibition/switching. FHx^{L} children showed no significant differences relative to TD children, and ASz children presented significantly lower verbal comprehension, and poorer scholastic achievement and verbal working memory. Scores obtained by the FHx^{H} and ASz children were similar on all tests except EF-category switching accuracy, where FHx^{H} children demonstrated more a prominent impairment. These results imply that by late childhood, children with one first-degree or two second-degree relatives with schizophrenia, and children presenting multiple well-replicated antecedents of schizophrenia, are characterised by cognitive impairment.

Deficits in verbal comprehension, verbal working memory, and scholastic achievement were observed among both FHx^{H} and ASz children, compared to the TD children. Low verbal comprehension and poor verbal working memory have been consistently identified in children and youth with a first-degree relative with

schizophrenia who have not yet passed through the age-range of risk for the disorder (Agnew-Blais and Seidman, 2013) and among UHR adolescents and young adults (Addington and Barbato, 2012, Fusar-Poli *et al.*, 2012b). These specific cognitive impairments may represent generalised risk markers for later psychosis that span genetic (i.e., individuals with a first-degree affected relatives) and clinical high-risk groups. The poor verbal abilities observed among both FHx^{H} and ASz children are in keeping with a previous investigation suggesting that verbal abilities may be one of the first cognitive processes to show impairment in children who subsequently develop schizophrenia (Reichenberg *et al.*, 2010).

Evidence from Chapter Three indicates that the extent to which poor school performance is associated with later schizophrenia is currently unclear. Among 16 year old offspring of adults with schizophrenia, two studies have reported an association between poor scholastic achievement based on end of year school assessment and family history of schizophrenia (Forsyth *et al.*, 2012, Jundong *et al.*, 2012), while there are no investigations of scholastic achievement among UHR individuals. Recent evidence supports an association between low scholastic performance and PLEs during childhood (Bartels-Velthuis *et al.*, 2011, Hameed *et al.*, 2013).

Meta-analysis in Chapter Four confirms that that lower than average premorbid IQ characterises children and adolescents who subsequently develop schizophrenia. Consistent with this finding, the results of the present study demonstrated that inclusion of full-scale IQ as a covariate in analyses of specific neurocognitive domains attenuated group differences, suggesting that specific cognitive impairments in FHx and ASz children were partly attributable to differences in general intellectual ability. However, adjusting for IQ in statistical analyses may lead to an underestimation of specific neurocognitive deficits, since some aspects of cognitive ability are correlated with IQ (Maccabe *et al.*, 2012).

The current findings demonstrate that children with differing profiles of risk for schizophrenia exhibit different degrees of neurocognitive impairment; those with a higher familial loading for schizophrenia were more cognitively impaired than children with lower familial loading, and children presenting with antecedents of schizophrenia. These results extend previous findings of greater neurocognitive impairment among youth with a first-degree compared to second-degree relatives with schizophrenia (Keshavan *et al.*, 2010) to children assessed well before the typical period of risk for development of the disorder.

FHx^{H} children, relative to TD children, additionally showed poor verbal memory, which is among the most robust impairment observed among children and young adults with affected first-degree relatives with schizophrenia and UHR individuals (Addington and Barbato, 2012, Agnew-Blais and Seidman, 2013, Fusar-Poli *et al.*, 2012b). Importantly, verbal memory deficits predict conversion to later psychosis among young offspring of individuals with schizophrenia and UHR youth (Brewer *et al.*, 2005, Erlenmeyer-Kimling *et al.*, 2000, Lencz *et al.*, 2006, Simon *et al.*, 2012, Woodberry *et al.*, 2010). Previous investigations directly comparing neurocognition in adolescents and young adults with first/second degree FHx relatives and UHR individuals observed verbal memory impairments in the FHx group (Myles-Worsley *et al.*, 2007) or the UHR group only (Seidman *et al.*, 2010). Methodological differences between studies make findings hard to aggregate; however, our findings, and those of a recent review of cognitive impairment among first-degree family members of affected individuals aged 30 years and younger (Agnew-Blais and Seidman, 2013), indicate that poor verbal memory may represent a possible genetic vulnerability indicator for schizophrenia.

Further, FHx^{H} children displayed impairment in additional cognitive domains that was not observed in FHx^{L} or ASz groups. Relative to the TD group, FHx^{H} children performed more poorly on two EF tasks, category switching accuracy and

inhibition/switching, indicating reduced cognitive flexibility. These findings are consistent with the poor cognitive flexibility widely observed among first-degree relatives of individuals who have yet to pass the age-range of risk typically associated with the disorder (Agnew-Blais and Seidman, 2013).

A previous investigation based on a smaller sample of ASz and TD children indicated lower full-scale IQ, verbal memory, and EF – inhibition scores in ASz children relative to TD children (Cullen *et al.*, 2010). The differences in results obtained across studies might be due to the smaller sample size or the inclusion in the ASz group of three children with a positive family history of schizophrenia (two FHx^{H} and one FHx^{L}). Moreover, in the present study, unlike the previous one, group comparisons controlled for ethnicity and parents' occupation. The prevalence of schizophrenia is higher among people of low socio-economic status and of African-Caribbean and black African ethnicity living in the UK (Fearon *et al.*, 2006, Tandon *et al.*, 2008b). Similarly, the prevalence ASz is higher among children of African-Caribbean and black African origin, than among white British children, living in the UK (Laurens *et al.*, 2011, Laurens *et al.*, 2008).

6.4.1 Strengths and Limitations

Strengths of the present study include the novel comparison of three groups at-risk for schizophrenia based on differing vulnerability profiles, the examination of children prior to the age typically associated with onset of the prodrome, and the broad array of neurocognitive tests employed. The small sample size may have limited our ability to detect neurocognitive impairments of small effect, and prohibited further examination of the role of confounding variables such as ethnicity in explaining group differences. Nonetheless, already in childhood, those with a first degree or two second-degree relatives with schizophrenia showed impairment across a range of cognitive domains consistent with several reviews of cognitive functioning in FHx adolescents

and young adults (Agnew-Blais and Seidman, 2013, Erlenmeyer-Kimling, 2000, Niemi *et al.*, 2003). While indexing family history as a continuous measure may theoretically provide more statistical power for detecting associations between liability and neurocognitive impairment, a categorical approach to indexing genetic liability identified two categories of children at-risk, and yielded similar results to a previous study that used both categorical and continuous definitions of family risk and identified similar neurocognitive impairments among non-ill relatives (Byrne *et al.*, 2003).

The TD group obtained mean IQ scores one SD above the US population means reported in the WASI (Wechsler, 1999). Mean IQ scores for ASz, $FHx^{H,}$ and FHx^{L} were around mean levels. By contrast, mean scores for the TD group on the scholastic achievement domain were in line with population means reported in the WIAT-II-UK (Wechsler, 2005). The WIAT-II-UK was the only cognitive measure to provide norms based on samples of children from the UK. The use of outdated and unrepresentative normative data in the WASI could over-estimate a child's IQ (Dethorne and Schaefer, 2004) and may not be appropriate for the sample in the present study.

6.4.2 Conclusion

Both children with a first-degree relative or two second-degree relatives with schizophrenia and those presenting a triad of antecedents showed impairments on neurocognitive tests relative to TD children. The impairments were explained largely by differences in IQ. By contrast, the performance of children with one second-degree affected relative on these tests was similar to that of TD children. If replicated, these findings may provide clues for identifying distinct aetiological factors active within each risk group, though verbal comprehension, scholastic achievement, and verbal working memory domains may confer generalised risk for psychosis across at-risk groups. Intervening to improve cognitive deficits in children at-risk for schizophrenia could alter the course of the developing illness. For example, among children with

deficits in working memory, a learning-based intervention has been shown to largely eliminate the deficit (Holmes et al., 2009). The evaluation of cognitive interventions with different risk groups of children may further understanding of aetiology while identifying strategies to increase resilience.

Chapter 7 Longitudinal changes in cognitive function from childhood to adolescence among youth at elevated risk for schizophrenia and spectrum disorders

7.1 Aim of study chapter

There are few prospective, longitudinal studies examining the developmental course of cognitive performance prior to the typical age of onset of prodromal symptomology. Consequently, it is not known whether children at-risk for schizophrenia, either because they present multiple antecedents of the disorder or because they have affected relatives, exhibit distinct patterns of change in cognitive performance over time. Among individuals who develop schizophrenia, childhood cognitive deficits appear to be relatively stable (Cannon *et al.*, 2002, Cannon *et al.*, 2000, Crow *et al.*, 1995), but may be characterised by a slower rate of growth particularly for verbal abilities (Reichenberg *et al.*, 2010). However, a decrement in IQ, scholastic achievement, processing speed, learning, and executive function has been reported as these individuals pass through adolescence and approach early adulthood (Ang and Tan, 2004, Bilder *et al.*, 2006, Caspi *et al.*, 2003, Fuller *et al.*, 2002, Jones *et al.*, 1994, Maccabe *et al.*, 2013, Meier *et al.*, in press, Osler *et al.*, 2007, Seidman *et al.*, 2006a, Seidman *et al.*, 2010).

The aim of the present study was to investigate changes in multiple domains of cognitive function from age 9 to 15 years among three groups of children: (1) ASz children characterised by a triad of well-replicated antecedents of schizophrenia; (2) FHx children with at least one affected relative; and (3) typically developing children (TD). Children were assessed three times: at baseline, and approximately 24- (FU24) and 48- months (FU48) later. To estimate cognitive change from age 9 to 15 years, exact age on the day of each cognitive assessment was included as a continuous predictor in statistical models. As a recent review of UHR studies indicated a typical

age of onset of basic prodromal symptoms of 16 years and over (Ruhrmann *et al.*, 2010), data from participants aged 16 years and older by the time of the third assessment (FU48) were excluded. It was anticipated that, between the ages of 9 and 15 years, ASz and FHx children, as compared to TD children, would exhibit differences in rate of change in IQ, scholastic achievement, memory, working memory, and executive function.

7.2 Method

7.2.1 Sample

7.2.1.1 Baseline assessments

One hundred and six children were recruited via school screening procedures or as relatives of patients receiving treatment within the South London and Maudsley National Health Service Foundation Trust, as described previously in Chapters Two and Three of the thesis. Briefly, antecedents of schizophrenia (ASz) comprised: (1) a child-reported "certainly-true" response on at least one of nine PLE items assessing hallucination- and delusion-like experiences (Laurens *et al.*, 2012); (2) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (Goodman, 2001); and (3) a caregiver-report of a motor and/or speech delay and/or abnormality (Laurens *et al.*, 2007). In contrast, TD children were defined as those who presented none of the three ASz criteria on screening questionnaires and who had no first-, second-, or third-degree relative with a schizophrenia spectrum disorder, as subsequently confirmed by FIGS interview with the child's primary caregiver (Maxwell, 1992).

Children with a family history of schizophrenia (FHx) included nine children with a first-degree relative with schizophrenia, two children with a first-degree relative with

schizoaffective disorder, two children each with two second-degree relatives with schizophrenia, and 16 children with one second-degree relative with schizophrenia confirmed on a FIGS interview (Maxwell, 1992) with the child's caregiver. The final sample consisted of 29 FHx, 32 ASz and 45 TD children. Children recruited into the study had never experienced a psychotic episode or taken anti-psychotic medication, and none presented with a neurological disorder, learning difficulties (IQ < 70), or a diagnosis of autism or Asperger's disorder.

Table 15 presents comparisons of demographic characteristics of the three groups of children at the baseline assessment. Groups were not significantly different on proportion of males or and handedness, but differed significantly on self-ascribed ethnicity and parent's occupational status.

Table 15. Comparison of demographic characteristics at baseline assessment (aged 9 to 12 years) for the longitudinal sample of ASz, FHx, and TD children

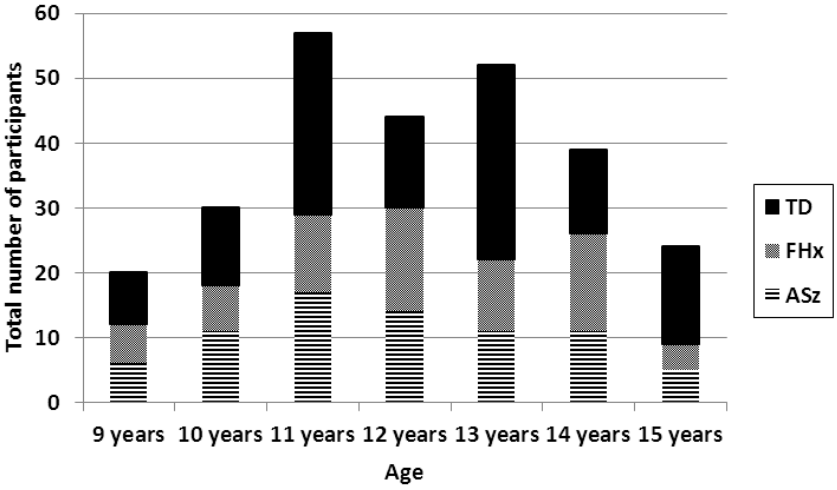
	ASz (n=29)		FHx (n=32)		TD (n=45)		Statistics
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Sex (Male)	22	(69)	12	(41)	21	(47)	X^2=5.4, (df=2), p=0.07
Laterality							*Fishers Exact Test*=1.7(df=2),
Right-hand dominance	25	(78)	26	(90)	39	(87)	
Mixed- or left-hand	7	(22)	3	(10)	6	(13)	
Ethnicity [a]							X^2=22.5, (df=4),p=<0.001
White	15	(47)	5	(17)	33	(73)	
Black African and African-Caribbean	9	(28)	14	(48)	7	(16	
Other	8	(25)	10	(35)	5	(11)	
Social Class based on parent's occupation[b]							X^2=23.7, (df=4), p=<0.001
Professional, managerial occupations	13	(41)	12	(41)	37	(82)	
Intermediate occupations	11	(34)	5	(18))	6	(13)	
Routine/manual occupations	8	(25)	12	(41)	2	(5)	

Notes: [a] "Black African and Black African-Caribbean" included children of mixed Asian- or white-Black African/African-Caribbean ethnicity. "Other" included children predominantly of other mixed ethnicities; and [b] Social class based on occupation (Office of Population Censuses and Surveys, 1980).

7.2.1.2 Follow-up assessments

Follow-up assessments were completed, on average, at two yearly intervals after the initial assessment of children at baseline (aged 9-12 years). Table 4 in Chapter Three, provides details of sample sizes at baseline, FU24, and FU48 assessments among ASz, FHx, and TD groups. At the FU24 and FU48 assessments, children completed the same antecedent screening questionnaires used to determine group assignments, in order to re-assess the two ASz triad components that could change over time (i.e., PLEs and social, emotional, and/or behavioural problems). At FU24, four (12.5%) ASz children obtained scores on the SDQ psychopathology subscales in the "normal" range based on UK population norms and they responded "not true" on all nine PLE items. At FU48, only one participant (3%) similarly no longer met ASz group criteria, and two (6.25%) ASz children had completed cognitive assessments when aged 16 years and older. Children who no longer met criteria for ASz group assignment and children 16 years or older were excluded from statistical analyses. Figure 8 illustrates the group sizes at each age year between 9 to 15 years (i.e., continuous data has been grouped into year categories for presentation only, but is retained in continuous format in statistical analyses).

Figure 8. Group numbers assessed within each year of age between 9 to 15 years



7.2.2 Procedure

Eligible children completed a battery of neurocognitive assessments in addition to biological and psychosocial measures, at each of the three assessments phases spaced at approximately two-year intervals, providing longitudinal data spanning from age 9-16 years. Ethical review of the study was provided by the Joint South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry Research Ethics Committee. At each assessment, children provided written assent and caregivers provided written informed consent for participation in the study.

7.2.3 Measures

7.2.3.1 Neurocognitive Assessments

A brief description of each measure for cognitive domains of IQ, scholastic achievement, memory, working memory and executive function is provided in Table 16.

In order to examine changes in cognitive performance through childhood and early adolescence, on all cognitive measures except IQ, raw scores were examined rather than manual derived age-standardised scaled scores.

Table 16. Details of neurocognitive measures administered

Neurocognitive measure	Test Description
Intelligence	
IQ (two subtest version)	
- Vocabulary	Define orally and visually presented words
- Matrix Reasoning	Choose one shape from five to complete a pattern
Scholastic Achievement	
- Word Reading	Read aloud a word list
- Numerical Operations	Complete mathematical problems
- Spelling	Write verbally presented words
Memory	
Verbal Memory	
- Story Memory	Immediate recall of details from two short stories read aloud
- Verbal Learning	Immediate free recall of word list (four trials)
Visual Memory	
- Design Memory	Immediate recall of five geometric designs
- Picture Memory	Identify differences between four similar pairs of pictures.
- Verbal Working Memory	Immediate recall of word lists by animal and non-animal categories
Executive Functioning	
Verbal Fluency	
- Letter Fluency	Generate words beginning with F, A, and S in 60s
- Category Fluency	Generate animals and boys' names in 60s
- Category Accuracy	Alternatively generate words from fruits and furniture categories in 60s
Colour Word interference	
- Inhibition	Name ink colour of colour words printed in different colour ink (Stroop, 1935).
- Inhibition/Switching	As for Inhibition subtest; or, reading colour word (ignore printed ink colour)
Towers Test	
- Towers Test Achievement score	Build towers using one to five pegs in the fewest possible number of moves

7.2.4 Statistical analyses

Univariate ANOVA and chi-square tests were used to compare groups on demographic variables. Longitudinal mixed models for repeated measures data were fitted to examine development of cognitive function between 9-15 years of age. The main predictors in all statistical models were group (ASz and FHx vs TD), fixed linear and quadratic effects of age, and interactions between linear and quadratic age and group; non-statistically significant quadratic terms were subsequently removed. Exact age at each assessment (baseline, FU24, and FU48) was fitted as a continuous predictor, centred in statistical analyses to 11 years (mean age of the total sample at baseline). In order to control for possible practice effects, an additional variable was created and entered into models to indicate whether an assessment were from a first or a follow-up assessment.

For each outcome a random-intercept and a random-coefficients model were fitted. A random effect of participant was specified in both models to account for correlations between repeated measurements on individuals over time. The random-coefficients model additionally contained a random slope of age and an unstructured covariance matrix. Models were fit by maximum likelihood estimation (MLE) and relative differences in goodness of fit between the two models were assessed using likelihood ratio tests. The simpler random-intercept model was selected unless the likelihood ratio test indicated that the random-coefficients model provided a better fit to the data.

Results were interpreted in line with previous work examining developmental changes in cognitive function among individuals from a population-based cohort who developed schizophrenia in adulthood (Reichenberg *et al.*, 2010). Group differences in performance at 11 years between ASz or FHx children relative to TD children were indicated by the mean intercept or starting point of slope. Differences in rate of change among ASz and FHx children relative to TD children were indicated by statistically

significant interactions between age (slope) and group. An initial increase in the positive gradient of the slope (significant interaction between linear age and group), which decreases with age was indexed by a negative quadratic slope value (interaction between quadratic age and group), suggesting a potential downward curve in cognitive development with increasing age, and a slower rate of change was indicated by a negative slope value (significant interaction between linear age and group).

Linear mixed model assumptions of normality and homogeneity of variance were checked by visual inspection of plots of residuals against fitted values. Line graphs of predicted values for measures of cognitive functions were plotted against age. All longitudinal mixed models were repeated incorporating ethnicity and parent's occupation at baseline assessment as covariates.

7.3 Results

As illustrated in Table 15, groups did not differ significantly on sex or laterality, but group status was significantly associated with ethnicity and parent's occupation. Mixed modeling parameter estimates, standard errors and p-values of fixed effects, and the type of statistical model fit for each neurocognitive measure are reported in Table 17. Results of analyses adjusted for ethnicity and parent's occupation are presented in Table 18.

Table 17. Parameter estimates of fixed effects for longitudinal mixed models of cognitive performance

	Estimated between group differences at 11 years of age		Estimated change per 1 year of age	Estimated between group differences in change per 1 year of age	
	ASz Vs TD	FHx Vs TD	TD	ASz Vs TD	FHx Vs TD
Subtest Measure	Estimate, SE; p-value	Estimate, SE; p-value	Estimate, SE; p-value	Estimate, SE; p-value	Estimate, SE; p-value
General Intelligence					
IQ	-10.90, 2.8; **<0.001**	-13.89, 2.9; **<0.001**	-2.47, 0.8; **0.001**	0.14, 1.3; 0.91	3.69, 1.2; **0.002**[c]
Scholastic Achievement					
Word Reading [a]	-7.51, 2.0; **<0.001**	-5.88, 2.1; **0.004**	2.31, 0.2; **<0.001**	0.85, 0.4; **0.04**	1.01, 0.4; **0.02**
Numerical Operations [a]	-5.43, 1.4; **<0.001**	-4.46, 1.5; **0.002**	2.35, 0.2; **<0.001**	-0.35, 0.4; 0.39	-0.37, 0.4; 0.36
Spelling [a]	-2.61, 1.4; **0.05**	-1.67, 1.4; 0.23	2.00; 0.2; **<0.001**	-0.19, 0.2; 0.44	-0.49, 0.3; **0.05**
Memory					
Verbal Memory	-9.79, 3.7; **0.008**	-16.61, 3.8; **<0.001**	1.31, 0.6; 0.06	3.04, 1.0; **0.002**	3.01, 1.0; **0.003**
Visual Memory [a]	-5.62, 2.4; **0.02**	-4.38, 2.5; 0.08	1.00, 0.4; **0.01**	0.61, 0.7; 0.36	-0.10, 0.7; 0.89
Verbal working memory	-3.82, 1.2; **0.002**	-4.33, 1.3; **0.001**	0.36, 0.2; 0.08	0.28, 0.4; 0.43	0.50, 0.3; 0.15
Executive Functioning					
Verbal Fluency					
Letter Fluency [a]	-2.92, 1.9; 0.13	-1.38, 2.0; 0.48	2.32, 0.3; **<0.001**	0.14, 0.5; 0.80	-0.34, 0.6; 0.54
Category Fluency	-2.40, 1.7; 0.15	-2.84, 1.7; 0.10	1.17, 0.3; **<0.001**	1.10, 0.5; **0.03**	-0.11, 0.5; 0.84
Category Accuracy	-1.31, 0.7; **0.05**	-2.39, 0.7; **0.001**	0.53, 0.1; **<0.001**	0.16, 0.2; 0.50	0.54, 0.2; **0.02**
Colour-word Interference [b]					
Inhibition	10.38, 3.5; **0.004**	14.89, 3.7; **<0.001**	-5.41, 0.6; **<0.001**	-2.66, 1.0; **0.009**	-3.06, 1.0; **0.003**
Inhibition/Switching [a]	7.60, 3.3; **0.02**	9.99, 3.4; **0.004**	-7.21, 1.2; **<0.001**	-4.35, 2.0; **0.03**	-4.97, 1.9; **0.008**[d]
Towers Test					
Towers Score	-0.74, 0.7; 0.26	-0.64, 0.7; 0.35	0.80, 0.2; **<0.001**	-0.25, 0.3; 0.33	-0.13, 0.3; 0.60

Notes: [a] Parameter estimates of fixed effects derived from random intercept and slope models; [b] Dependent variable is task completion time measured in seconds, where negative values indicate quicker task completion time and positive values indicate slower task completion time; [c] interaction between FHx group and quadratic centred age (-0.78, 0.3; **0.02**); and [d] interaction between FHx group and quadratic centred age (-1.01, 0.5; **0.05**).

Table 18. Parameter estimates of fixed effects for longitudinal mixed models of cognitive performance adjusted for ethnicity and parent's occupation.

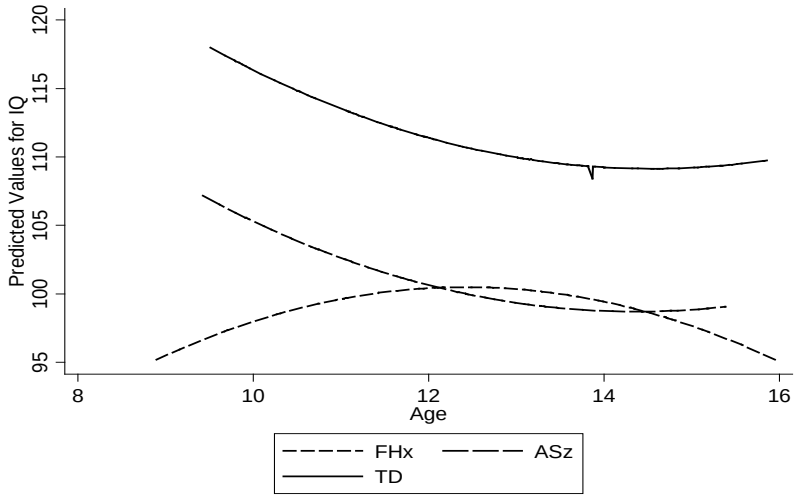
	Estimated between group differences at 11 years of age		Estimated change per 1 year of age	Estimated between group differences in change per 1 year of age	
	ASz Vs TD	FHx Vs TD	TD	ASz Vs TD	FHx Vs TD
Subtest Measure	Estimate, SE; p-value	Estimate, SE, p-value	Estimate, SE; p-value	Estimate, SE; p-value	Estimate, SE; p-value
General Intelligence					
IQ	-5.34, 2.5; **0.03**	-5.07, 2.8; 0.07	-2.44, 0.8; **0.001**	-0.05, 1.3; 0.97	3.29, 1.2; **0.005**[c]
Scholastic Achievement					
Word Reading [a]	-5.24, 2.0; **0.007**	-2.46, 2.1; 0.24	2.33, 0.2; **<0.001**	0.90, 0.4; **0.03**	0.94, 0.4; **0.03**
Numerical Operations [a]	-2.91, 1.4; **0.03**	-0.80, 1.5; 0.60	2.33, 0.2; **<0.001**	-0.37, 0.4; 0.36	-0.37, 0.4; 0.36
Spelling [a]	-1.12, 1.4; 0.41	0.07, 1.4; 0.96	2.00, 0.2; **<0.001**	-0.14, 0.2; 0.58	-0.48, 0.3; 0.06
Memory					
Verbal Memory [a]	-3.1, 3.5; 0.37	-4.92, 3.9; 0.20	1.33, 0.6; 0.06	3.17, 1.0; **0.001**	2.71, 1.0; **0.006**
Visual Memory	-3.49, 0.4; 0.14	0.11, 2.7; 0.97	0.98, 0.4; **0.01**	0.71, 0.7; 0.28	-0.15, 0.7; 0.82
Verbal working memory	-2.63, 1.3; **0.04**	-2.32, 1.4; 0.10	0.36, 0.2; 0.08	0.29, 0.4; 0.41	0.44, 0.3; 0.20
Executive Functioning					
Verbal Fluency					
Letter Fluency [a]	-2.02, 1.9; 0.30	-0.56, 2.1; 0.80	2.32, 0.3; **<0.001**	0.17, 0.5; 0.76	-0.36, 0.6; 0.52
Category Fluency	-0.44, 1.7; 0.79	0.38, 1.9; 0.84	1.16, 0.3; **0.001**	1.15, 0.5; **0.02**	-0.21, 0.5; 0.68
Category Accuracy	-0.62, 0.7; 0.35	-1.16, 0.8; 0.21	0.54, 0.1; **<0.001**	0.18; 0.2; 0.44	0.51, 0.2; **0.03**
Colour-word Interference [b]					
Inhibition [a]	6.68, 3.6; **0.05**	10.41, 3.9; **0.01**	-5.40, 0.6; **<0.001**	-2.75, 1.0; **0.007**	-3.02, 1.0; 0.003
Inhibition/Switching [a]	7.46, 3.5; **0.03**	10.27, 3.6; **0.009**	-7.23, 1.2; **<0.001**	-4.31, 2.0; **0.03**	-4.96, 1.9; 0.008[d]
Towers Test					
Towers Score	-0.17, 0.7; 0.80	0.32, 0.8; 0.67	0.80, 0.2; **<0.001**	-0.24, 0.2; 0.34	-0.19, 0.2; 0.46

Notes: [a] Parameter estimates of fixed effects derived from random intercept and slope models; [b] Dependent variable is task completion time measured in seconds, where negative values indicate quicker task completion time and positive estimate values indicate slower task completion time; [g] interaction between FHx group and quadratic centred age (-0.67, 0.3; **0.03**); and [h] interaction between FHx group and quadratic centred age (-1.00, 0.5; **0.05**).

7.3.1 General Intelligence

The IQ of the TD group significantly decreased by 2.4 points per year. At 11 years, ASz youth exhibited a lower IQ compared to TD youth with no significant difference in change of IQ with age indicating that the lower IQ at age 11 remained significantly lower to age 15. This pattern of results remained after adjustment for ethnicity and parent's occupation. FHx children, relative to TD children, displayed a significantly lower IQ at 11 years. Initially, the FHx group exhibited a statistically significant increase in IQ relative to TD children, but with age this improvement in IQ was followed by a significant slowing in rate of improvement (see Figure 9). Among FHx youth, only differences in rate of change remained significant after including ethnicity and parent's occupation in models.

Figure 9. Line graph of predicted values for IQ



7.3.2 Scholastic Achievement

Both ASz and FHx children demonstrated significantly lower word reading scores at 11 years and a faster rate of improvement with age compared to the TD group (see Figure 10). Results remained the same after adjusting for ethnicity and parent's occupation, except that the initial differences between FHx and TD youth at 11 years were attenuated. Relative to TD youth, ASz and FHx individuals displayed lower

numerical operations scores at 11 years and no difference in age-related change (Figure 11). Among FHx youth, results were no longer significant after the incorporation of covariates in analyses.

Figure 10. Line graph of predicted values for word reading scores

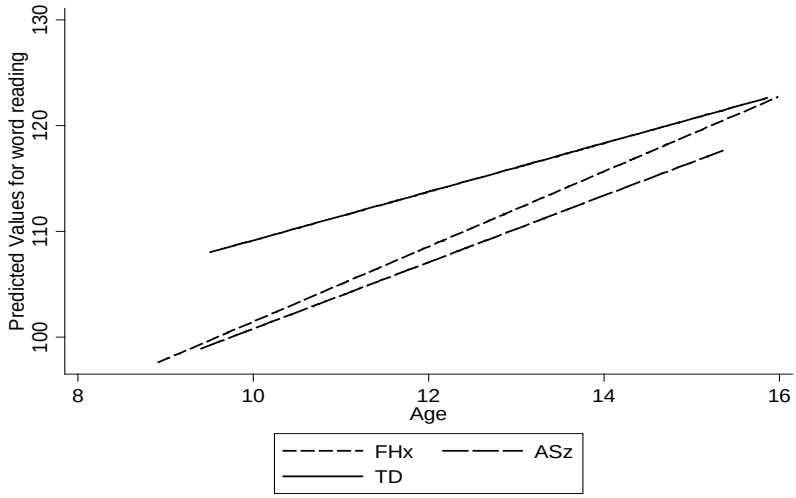
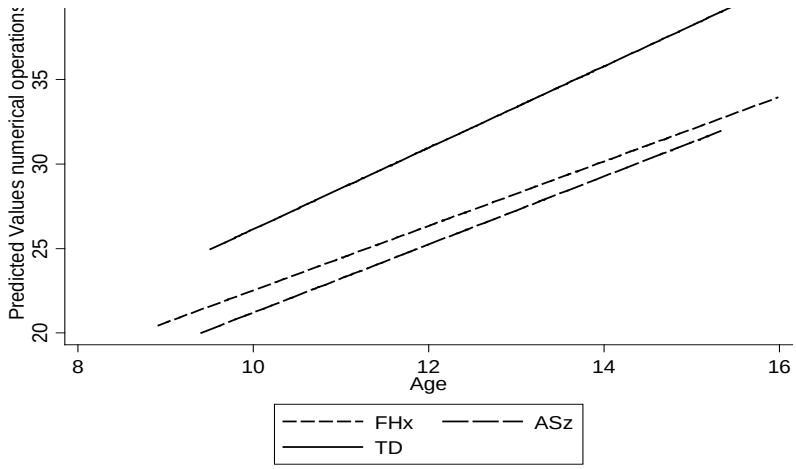


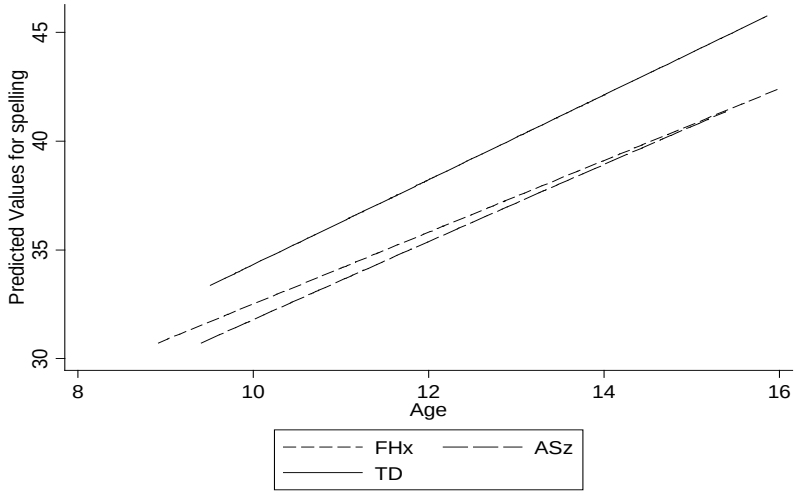
Figure 11. Line graph of predicted values for numerical operations



Compared to the TD children, ASz children displayed poorer spelling scores at 11 years and no difference in rate of improvement with age. In contrast, no differences were observed between the FHx and TD children on spelling scores at 11 years, but FHx individuals were characterised by a significantly slower rate of change (see Figure 12). After the adjustment for covariates in the models, ASz children no longer displayed

poorer spelling at 11 years and FHx individuals demonstrated a trend level slower rate of rate of change relative to TD group.

Figure 12. Line graph of predicted values for spelling



7.3.3 Memory

As illustrated in Figure 13, both ASz and FHx groups displayed significantly lower verbal memory scores at 11 years and a faster rate of improvement with age compared to TD youth. Only rates of change remained significant after the inclusion of ethnicity and parent's occupation in statistical analyses. On the test of visual memory, ASz children, relative to TD children, obtained significantly lower scores at 11 years and showed no difference in change over the subsequent years (see Figure 14). The difference at 11 years was no longer significant after the adjustment for ethnicity and parent's occupation in statistical models. On the test of visual memory, FHx children as compared to TD children showed no difference in performance at 11 years nor in the rate of change.

Figure 13. Line graph of predicted values for verbal memory

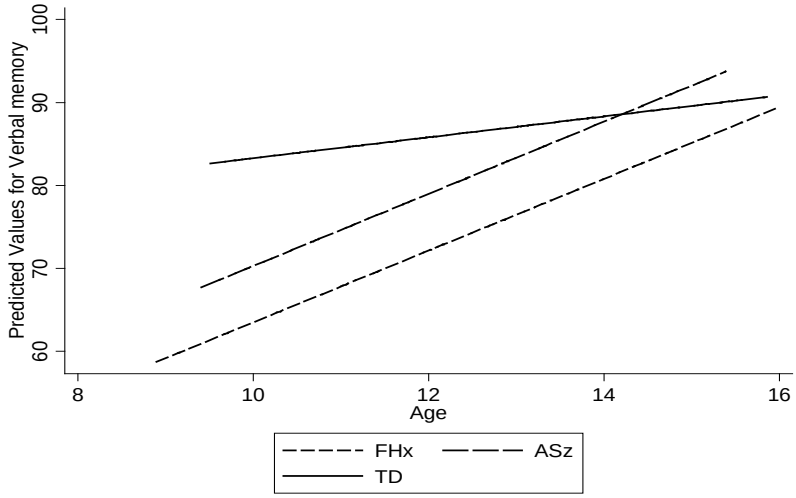
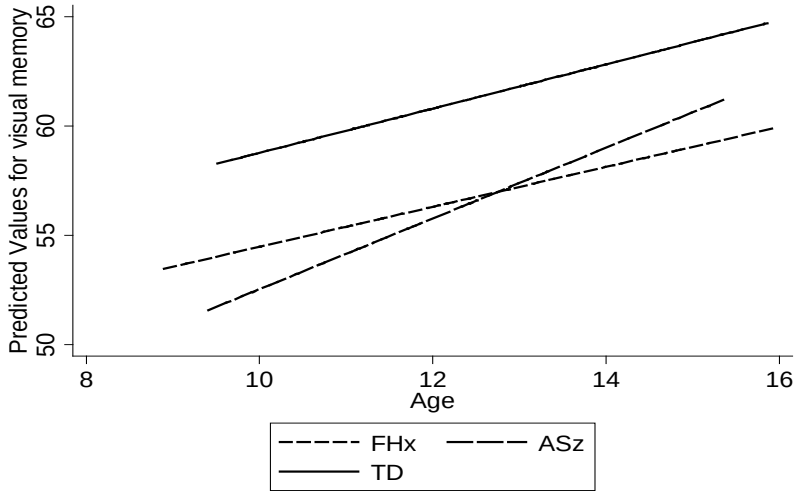
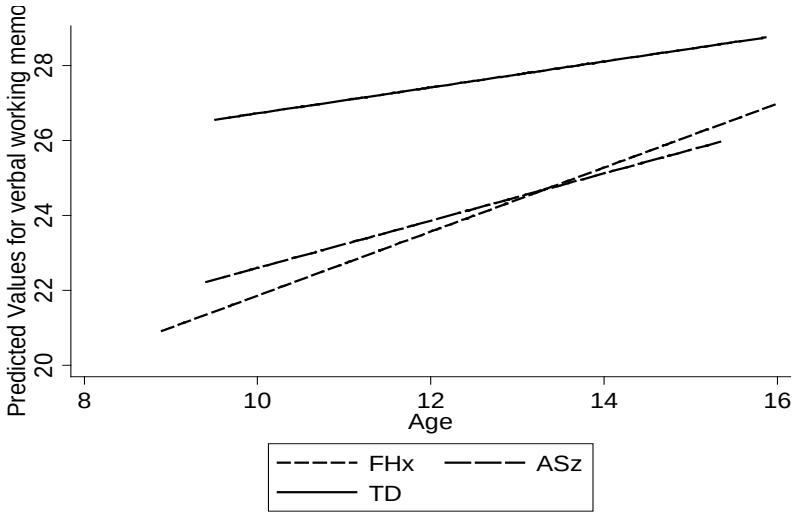


Figure 14. Line graph of predicted values for visual memory



Relative to the TD group, ASz and FHx groups exhibited significantly lower verbal working memory scores at 11 years and no differences in rate of improvement over the subsequent years (see Figure 15). After incorporating ethnicity and parent's occupation in statistical models no differences were observed between FHx and TD groups at 11 years old.

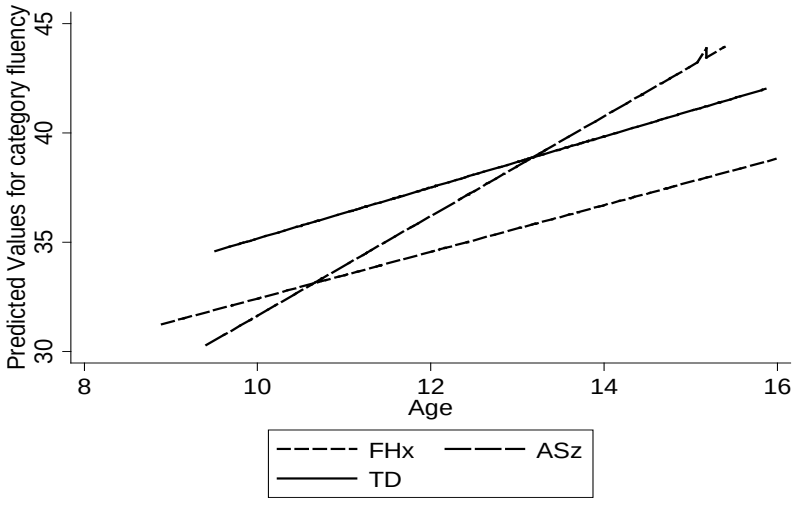
Figure 15. Line graph of predicted values for verbal working memory



7.3.4 Executive Function

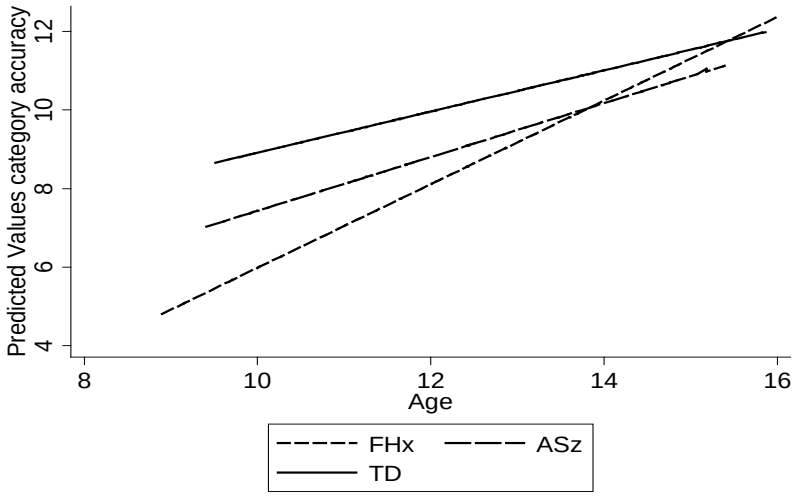
Longitudinal mixed models unadjusted and adjusted for ethnicity and parent's occupation indicated no differences in performance at 11 years or in the rate of change for letter fluency and towers test measures of the ASz and FHx children relative to the TD children, or in category fluency of the FHx children compared to TD children. On the category fluency measure (Figure 16), no differences at age 11 years were observed among ASz youth but a faster rate of improvement compared to TD children was found which remained significant after adjusting for ethnicity and parent's occupation.

Figure 16. Line graph of predicted values for category fluency



As shown in Figure 17, ASz and FHx youth had significantly lower category accuracy scores at 11 years than the TD children. The ASz group showed no differences in rate of change while the FHx group showed a significantly faster rate of improvement than the TD group. Relative to TD group, ASz and FHx differences at 11 years were no longer significant after adjusting for ethnicity and parent's occupation.

Figure 17. Line graph of predicted values for category accuracy



Relative to TD children, both ASz and FHx groups displayed slower inhibition task completion times at 11 years and significantly faster rates of change with increasing age (Figure 18). ASz and FHx youth displayed significantly slower inhibition/switching task completion times at 11 years compared to TD group. Relative to TD group, ASz children showed faster rates of change with age whilst FHx youth exhibited significantly faster rates of improvement from 11 years, which was followed by a slowing in rate of improvement (Figure 19). Results for inhibition and inhibition/switching measures remained the same after adjusting models for ethnicity and parent's occupation.

Figure 18. Line graph of predicted values for inhibition completion time

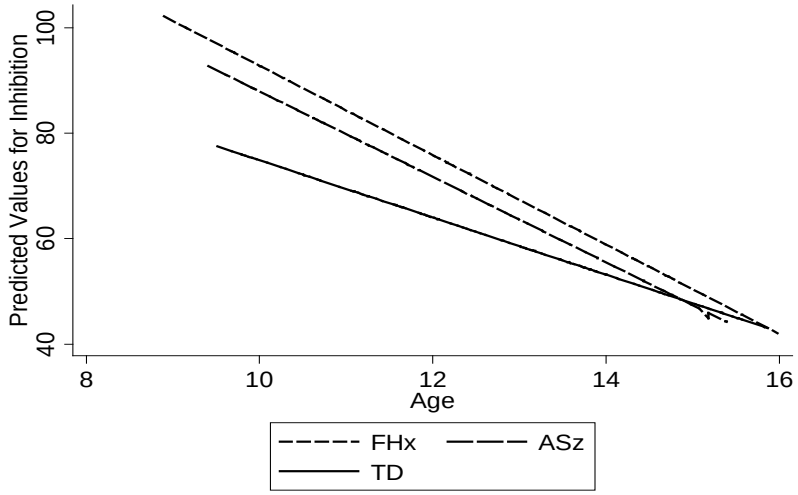
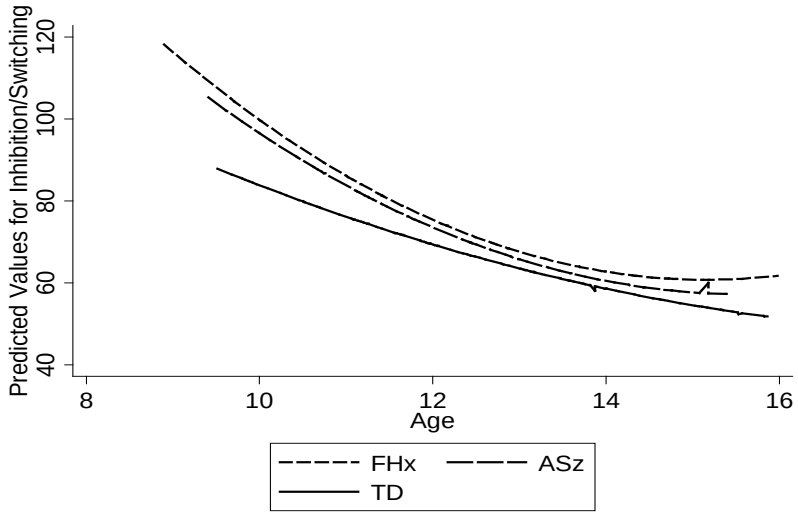


Figure 19. Line graph of predicted valued for inhibition/switching completion time



7.4 Discussion

The aim of this investigation was to examine the developmental course of cognitive performance from childhood into adolescence among children characterised by a triad of well-replicated antecedents of schizophrenia and children with affected relatives, relative to typically developing children. Several important findings emerged. One, results unadjusted for ethnicity and parent's occupation indicated that ASz and FHx youth presented impairments in scholastic achievement (word reading and numerical operations measures) and verbal working memory from age 9 to 15 years compared to TD children. Two, ASz children were additionally characterised by lower IQ, poorer

performance on spelling (scholastic achievement domain) and EF- category accuracy measure from age 9 to 15 years. Three, the FHx group demonstrated a slower rate of improvement in spelling than the TD children. Four, FHx youth experienced initial increases in IQ and the EF-inhibition/switching measure relative to TD children, narrowing the observed gap between the two groups at age 11 years, but over time this relative increase slowed and differences between FHx and TD groups widened again. Five, ASz and FHx children showed improvement in scores obtained on measures of verbal memory and EF (category fluency, category accuracy, inhibition, and inhibition/switching) to levels similar to those achieved by the TD children by age 15 years. Thus, two groups of children at-risk for schizophrenia, one group presenting multiple antecedents of the disorder and the other having affected relatives, were characterised by cognitive impairments and differing patterns of longitudinal change from age 9 to 15 years relative to TD children.

Between the ages of 9 and 15 years, ASz youth exhibited a stable IQ deficit relative to TD children. This result is consistent with findings from the meta-analyses presented in Chapter Four which indicated that, prior to 13 years and up to 16 years, individuals who later developed schizophrenia displayed lower IQ compared to individuals who remained healthy. By contrast, FHx children showed an initial improvement in IQ during late childhood, but the rate of this increase slowed, widening the gap between FHx and TD groups. A decline in IQ between 5 and 16 years has also been observed among children with a parent with schizophrenia (Worland *et al.*, 1982) and, in a longitudinal study of first-and second-degree relatives aged 16 to 25 years of individuals with schizophrenia, the development of psychotic symptoms was preceded by a decline in IQ and verbal memory (Cosway *et al.*, 2000). Typically, adults with schizophrenia display IQ impairments that are larger in magnitude than impairments observed among child/adolescent offspring of adults with schizophrenia (Caspi *et al.*,

2003, Maziade *et al.*, 2008, Seidman *et al.*, 2006a). This evidence implies that further IQ decline may take place later in development, closer to the time of onset of the prodrome (Cosway *et al.*, 2000, Maziade *et al.*, 2011a).

The Flynn effect (Flynn, 1987) refers to the rise in IQ scores observed in the population over time, leading to inflated IQ scores being obtained when using normative data that were assembled more than 15 years previously to assessment (Dethorne and Schaefer, 2004). This effect may be more or less pronounced at different ages (Kanaya *et al.*, 2005) and different levels of cognitive ability (Sanborn *et al.*, 2003). However, the TD and ASz group both experienced an approximate 2 point decline in IQ per year. A non-significant decline in full-scale IQ based on the full (four-subtest) WASI assessment, and a significant decline in verbal IQ (derived from two WASI subtests), was recently observed among healthy children aged 6-18 years over three assessment phases conducted at two-year intervals (Waber *et al.*, 2012). Thus, the use of outdated and small normative sample sizes (comprising approximately 30 individuals between ages 6 to 16 years) within the WASI (Wechsler, 1999) may have obscured our ability to characterise group differences in IQ.

Alternatively, the decline in IQ observed for all three groups may reflect early cannabis use. Cross-sectional studies indicate that poor cognitive function is associated with a younger age of onset of cannabis use (Fontes *et al.*, 2011, Gruber *et al.*, 2012, Pope *et al.*, 2001). Recent evidence from a prospective birth cohort study reported a decline in IQ from childhood into adulthood among adolescent-onset cannabis users (Meier *et al.*, 2012). Unfortunately, cannabis use was not assessed in the current study. Further investigation is needed to determine the role of cannabis use on the developmental course of multiple cognitive functions.

However, caution is recommended when interpreting the findings of intellectual trajectories in the present study. Large increases and decreases in IQ during childhood

and adolescence have previously been reported in longitudinal studies originating in the early 1900's (Honzik *et al.*, 1948, Sontag *et al.*, 1958). In addition, longitudinal studies examining IQ change based on greater than two repeated IQ measurements have reported considerable intra-individual differences in IQ trajectories during development (Hindley and Owen, 1979, Mccall *et al.*, 1973, Ramey *et al.*, 1989). One study examining changes in IQ score between 7, 9, 11, and 13 years based on 794 individuals from the Dunedin cohort, New Zealand concluded that for the most children, IQ change was minimal or due to psychometric measurement error (Moffitt *et al.*, 1993). A minority of these children (n=107) experienced substantial change in IQ scores across each time point, that did not reflect measurement error. Among these children, observed IQ changes were not related to individual differences or family factors, which may have been putatively associated to significant IQ change such as behavioural issues, maternal mental health, or changing residence and schools (Moffitt *et al.*, 1993). The authors conclude that "real" IQ change during childhood and adolescence is highly variable, personal, transient, and not associated with environmental change.

Poor scholastic achievement observed among ASz and FHx youth compared to TD children is congruent with findings from the 1956 British Birth cohort which reported stable deficits in reading and mathematics from age 7 to age 11 years, and to age 16 years among individuals who later developed schizophrenia (Crow *et al.*, 1995). However, declining verbal abilities and scholastic achievement during late adolescence may also be associated with the development of schizophrenia (Ang and Tan, 2004, Bilder *et al.*, 2006, Fuller *et al.*, 2002, Jones *et al.*, 1994, Maccabe *et al.*, 2013).

ASz children were characterised by persistent PLEs which may contribute to academic difficulties in school. A previous study found that persistent auditory PLEs among children aged 7 to 8 years were associated with poor scholastic achievement 5 years later (Bartels-Velthuis *et al.*, 2011). More recently, another investigation reported

that consistently low and declining literacy skills in childhood were associated with suspected and definite PLEs at 12 years (Hameed *et al.*, 2013).

FHx children, relative to TD children, showed a slower rate of change in scores obtained on spelling. The process of learning to spell requires effective encoding of words in memory. Consequently, difficulties in encoding processes may account, at least in part, for the slower improvement in spelling observed among the FHx youth. Therefore, it is plausible that poor scholastic ability may reflect stable impairments in other cognitive domains such as verbal working memory. Indeed, among healthy children and adolescents, verbal working memory skills predict performance in other cognitive areas including scholastic achievement (Gathercole *et al.*, 2004). Cross-sectional investigations have consistently identified poor verbal working memory among children with a first-degree relative with schizophrenia (Agnew-Blais and Seidman, 2013), and among youth meeting UHR criteria (Addington and Barbato, 2012, Fusar-Poli *et al.*, 2012b). Stable impairments in verbal working memory between 9 and 12 years have also been demonstrated among offspring of a parent with schizophrenia as compared to typically developing children assessed only once at 11 years (Ross *et al.*, 2008). More recently, poor working memory at 8 and 10 years has been reported as being associated with a greater risk of PLEs at 12 years (Niarchou *et al.*, 2013). The presence of a stable deficit in verbal working memory among both ASz and FHx youth provides further evidence that this particular cognitive dysfunction may be a robust childhood risk factor of schizophrenia. However, future studies are needed to test this hypothesis as presently nothing is known about the proportion of children with ASz who will develop schizophrenia or SSD, nor about the characteristics that differentiate the FHx children who develop these disorders.

Cross-sectional assessments conducted in healthy individuals aged between 8 and 21 years, suggests that verbal memory capacities peak by 8 years (Gur *et al.*, 2012).

Results from the present study indicated that TD children did not show significant improvements in verbal memory between ages 9 to 15 years, suggesting that they may have already achieved their maximum performance capacity. In contrast, ASz and FHx children demonstrated significantly faster rates of change with age. Although speculative, the faster rate of improvement or 'catch-up' in verbal memory performance among the ASz and FHx youth may reflect the delayed maturation of temporal lobe structures. Volumetric abnormalities in the temporal lobe have been reported among ASz children aged between 9 to 12 years (Cullen *et al.*, 2013) and among at-risk youth with a family history of schizophrenia (Johnstone *et al.*, 2005).

Among healthy children and adolescents, EF abilities develop later and continue to develop over a longer period of time than other cognitive functions, consistent with ongoing maturation and myelination of the frontal lobes during adolescence (Anderson *et al.*, 2001, Giedd *et al.*, 1999). In line with existing evidence regarding the development of EF during adolescence (Best and Miller, 2010), TD children exhibited an improvement on all EF measures. A recent review examining evidence for schizophrenia as a disorder of neurodevelopment postulated that schizophrenia should be considered in the context of differing trajectories of EF (Catts *et al.*, 2013). Indeed, ASz youth, as compared to TD youth, exhibited a stable deficit in category accuracy and significant improvements with age on measures of category fluency, inhibition, and inhibition/switching. By contrast, FHx children displayed similar significant improvement on the category accuracy and inhibition subtests. Thus, the ASz and FHx youth developed some aspects of executive function slightly later than TD youth.

On the inhibition/switching measure, FHx youth displayed faster improvement than the TD youth, but the initial increase on the positive gradient of the slope decreased over time and plateaued. Deficits in performance on the Stroop test, a colour-word interference measure, are observed consistently among adults with schizophrenia and to

a lesser extent among unaffected first-degree relatives of individuals with schizophrenia (Reichenberg and Harvey, 2007). Further follow-up assessments extending into later adolescence are required to determine whether this plateau will remain stable or whether a decline in the set-shifting abilities may begin as the prodrome approaches. However, findings from the present study provide further evidence that different EF abilities may have distinct developmental courses (Best and Miller, 2010, Freedman and Brown, 2011).

After adjusting statistical models for ethnicity and parent's occupation, overall differences between the ASz and TD and the FHx and TD youth were attenuated. Among the ASz youth, relative to the TD youth, statistically significant stable deficits over time remained on IQ, tests of scholastic achievement (word reading and numerical operations), and verbal working memory. By contrast, differences in rates of change in performance of both the ASz and FHx youth compared to TD youth remained statistically significant after entering the two covariates into the statistical models. Income-related differences may play in an important role in cognitive development such that children from high income backgrounds perform significantly better than individuals from low income backgrounds on a wide range of cognitive measures (Waber *et al.*, 2007, Waber *et al.*, 2012). Findings from the present study indicate that SES differences play an important role in cognitive performance during childhood.

Both ethnicity and low socio-economic status of the family of origin are risk factors for schizophrenia (Maccabe, 2008). Within the ASz and FHx groups, some children will likely develop schizophrenia or SSD while others will not. Those children who will develop these disorders are more likely than the others to be characterised by poorer cognitive performance and to have parents of African-Caribbean ethnicity with low-paying occupations. Thus, the inclusion of these covariates in the analyses may render

the tests of statistical significance overly conservative, as these factors are part of the inherent risk associated with development of schizophrenia and SSD.

7.4.1 Strengths and Limitations

The present study is characterised by three principle strengths. First, the assessment of cognitive change during childhood and into early adolescence prior to the age-range of risk associated with the development of schizophrenia. Secondly, the inclusion of a typically developing group, thereby, providing information on the trajectory of normal cognitive development as a basis for identifying specific abnormalities that maybe associated with risk for the disorder. Thirdly, the use of repeated assessments using the same cognitive measure.

These findings should be interpreted in light of some limitations. A small sample, particularly at the third assessment (FU48) may have compromised the robustness of our results. However, in contrast to other statistical procedures for analysing longitudinal data such as repeated measures analysis of covariance, longitudinal mixed modelling is not limited by partially missing data or unequally spaced assessments and is characterised by increased statistical power (Curran *et al.*, 2010). A further limitation was the small number of FHx children, which did not permit us to differentiate between those with high and low family loading for schizophrenia, as was done in the previous study of cognitive performance at the initial assessment (Chapter Six). It is possible that children with a higher familial loading for schizophrenia, defined as having one first-degree or two second-degree relatives with the disorder, may present a different developmental course of cognitive function to those with a low familial loading defined as having one second-degree relative only. Thus, it is not clear whether the incorporation of youth with high and low familial loading into one FHx group obscured different trajectories of cognitive development within this group.

7.4.2 Conclusions

This prospective longitudinal study is the first to examine the development of cognitive functions among youth at-risk for schizophrenia and SSD by virtue of the presence of antecedents or affected relatives as compared to TD youth. During childhood and adolescence, cognitive development appears to be highly variable; characterised by periods of little change, rapid increases, and for some measures, a decrease in rates of improvements (Catts *et al.*, 2013, Waber *et al.*, 2012). Evidence of differences in trajectories of cognitive performance across a broad range of cognitive measures highlights the importance of examining age-related changes in cognitive function among youth at-risk for schizophrenia. Follow-up of the ASz and FHx children assessed in the present study is necessary to establish the extent to which these differing trajectories of cognitive development may indicate differences in risk for schizophrenia and SSD. It has been suggested that differences in rates of change of cognitive functions among youth at-risk for schizophrenia may indicate differing capacities for neural plasticity and targets for remediation (Maziade *et al.*, 2011a). Moreover, cognitive remediation programmes that target specific working memory deficits in schizophrenia may also be effective across a range of cognitive domains (Holmes *et al.*, 2009, Witt, 2011).

Section 2: Facial emotion processing abnormalities

Chapter 8 Literature review: Facial emotion processing abnormalities among youth at-risk for schizophrenia

8.1 Aims of chapter

The purpose of the following chapter is to clarify the extent to which facial emotion processing impairments characterise youth at elevated risk for the development of schizophrenia. This review focuses on studies of facial emotion processing function among young non-ill relatives of adults with schizophrenia, studies of youth meeting UHR criteria, and children/adolescents reporting PLEs.

8.2 Facial emotion processing abnormalities

Poor social functioning is a hallmark of schizophrenia (Addington *et al.*, 2006). Studies of adults with schizophrenia have demonstrated that facial affect recognition is related to aspects of social functioning, such as social skills, general social functioning and quality of life (Couture *et al.*, 2006, Fett *et al.*, 2011, Hooker and Park, 2002, Kee *et al.*, 2003, Mueser *et al.*, 1996). Facial emotion expressions represent nonverbal social cues used to direct social interactions and to ensure appropriate social responses or behaviour. Thus, a number of problems may result from difficulties in identifying emotions in the faces of others. For example, the misinterpretation of facial affect by adults with schizophrenia is a potential mechanism leading to symptoms of schizophrenia such as delusions and social withdrawal (Frith, 1992, Marwick and Hall, 2008).

There is robust evidence of facial emotion recognition and discrimination impairments, particularly for negative emotions, among adults with schizophrenia and individuals experiencing FEP (Addington *et al.*, 2008, Amminger *et al.*, 2012, Edwards *et al.*, 2001, Kohler *et al.*, 2010, Mandal *et al.*, 1998, Pinkham *et al.*, 2007, Thompson *et al.*, 2012). Adults with schizophrenia are also more impaired in face emotion processing

than adults with affective disorders, suggesting some degree of specificity (Addington and Addington, 1998, Edwards *et al.*, 2001). To better characterise the nature of face emotion recognition (FER) in schizophrenia, several studies have examined emotion misperceptions. An examination of the types of errors made during FER tasks could provide important information concerning cognitive-perceptual processes contributing to facial emotion processing difficulties. Unfortunately, the majority of FER studies do not provide information on the nature of facial emotion misperceptions; however, individuals with schizophrenia appear to more often mislabel negative emotions as neutral expressions relative to healthy individuals (Kohler *et al.*, 2003, Premkumar *et al.*, 2008). The tendency to misinterpret neutral facial expressions as displaying emotion may contribute to the development of positive symptoms (Seiferth *et al.*, 2008) and is consistent with the theory that the development of schizophrenia involves the aberrant assignment of salience to insignificant stimuli (Kapur, 2003).

Findings from longitudinal investigations of adults with schizophrenia imply that facial emotion processing difficulties may represent a stable trait (Addington *et al.*, 2008, Addington *et al.*, 2012, Wolwer *et al.*, 1996). Moreover, these difficulties appear to effect psychosocial functioning independently of the presence of positive and negative symptoms (Kohler and Martin, 2006). Presently it is not clear if difficulties in recognising emotions in the faces of others are present among youth at-risk for schizophrenia, or whether these impairments may represent markers of risk for development of the disorder. Since difficulties with FER contribute to the poor social functioning observed among adults with schizophrenia (Marwick and Hall, 2008), it may be that poor FER is associated with the declining social and role functioning that characterises the prodromal period, and also premorbid social impairments among youth who subsequently develop schizophrenia (Welham *et al.*, 2009a). Interventions to improve FER performance (e.g., Training of Affect Recognition) among adults with

schizophrenia can reduce these deficits and elicit generalised improvements in other social cognitive domains (Wolwer and Frommann, 2011). Such interventions may also benefit youth at-risk for the disorder. Table 19 below describes studies examining facial emotion processing among individuals aged 30 years with a positive family history of schizophrenia or SSD, youth meeting UHR criteria, and children/adolescents experiencing PLEs. Effect sizes are presented for at-risk group relative to healthy comparison individuals only and were obtained from primary study or calculated using means and SDs provided unless specified (negative values indicate lower performance in at-risk group).

8.2.1 Individuals with a positive family history of schizophrenia

A recent meta-analyses of social cognition among first-degree relatives of individuals with schizophrenia reported a moderate effect size impairment (d=0.42) on facial emotion processing tasks (Lavoie *et al.*, 2013), that are smaller in magnitude than FER impairments observed among adults with schizophrenia (Kohler *et al.*, 2010). These findings indicate that, to some extent, FER may be a heritable risk factor for later schizophrenia. However, the majority of studies included in the meta-analyses comprised of individuals who had already passed through the age range of risk associated with schizophrenia. Table 19 at the end of this Chapter outlines those studies examining FER in unaffected relatives aged < 30 years only relative to healthy comparison groups.

Evidence for a FER impairment among young unaffected first-degree relatives of adults with schizophrenia is mixed (Barbour *et al.*, 2010, Bölte and Poustka, 2003, Davalos *et al.*, 2004, De Achával *et al.*, 2010, Eack *et al.*, 2010, Li *et al.*, 2012, Li *et al.*, 2010, Meijer *et al.*, 2012). Eack and colleagues found that unaffected adolescent offspring of parents with schizophrenia or SSD were impaired in recognising of neutral faces only, and over-attributed emotions to neutral faces, primarily mislabelling neutral

faces as sad (Eack *et al.*, 2010). Methodological differences across studies may account for the inconsistency of findings. Indeed, there appears to be little continuity across studies particularly with regard to FER paradigm and emotion stimulus (Edwards *et al.*, 2002). Of the eight studies included in Table 19, that examined FER among young first-degree relatives of individuals with schizophrenia or SSD none used the same paradigm and only four studies used the same emotion stimuli (Barbour *et al.*, 2010, Bölte and Poustka, 2003, Li *et al.*, 2012, Li *et al.*, 2010); namely, black and white photos from the Pictures of Facial Affect collection (Ekman *et al.*, 1972) which are typically restricted in ethnicity and age (Gur *et al.*, 2002). Further, Lavorie and colleagues compared studies examining FER between parents and siblings of individuals with schizophrenia (Lavoie *et al.*, 2013). Results indicated larger effect sizes for parents relative to siblings of adults with schizophrenia which may reflect the use of poorly age-matched comparison groups in FER studies.

Nonetheless, this evidence indicates that FER difficulties may not characterise young unaffected relatives of individuals with schizophrenia, though these individuals show deficits in other aspects of social cognition (Gibson *et al.*, 2010). It is plausible that FER abnormalities in FHx youth are more subtle requiring FER paradigms that allow the examination of misperceptions of emotions in faces and emotional stimuli involving low intensity expressions (Phillips and Seidman, 2008).

8.2.2 Symptomatic, help-seeking individuals meeting Ultra High-Risk criteria

Table 19 provides an overview of the few studies that have examined FER among UHR youth relative to schizophrenia and healthy comparison groups. As with studies of young unaffected relatives of individuals with schizophrenia or SSD, cross-sectional investigations indicate that evidence for an FER impairment among UHR youth is inconclusive (Addington *et al.*, 2008, Amminger *et al.*, 2012, Pinkham *et al.*, 2007, Thompson *et al.*, 2012, Van Rijin *et al.*, 2011). Two studies reported differences in FER

between schizophrenia and FEP groups relative to healthy individuals but not between individuals meeting UHR criteria and healthy comparison groups (Pinkham *et al.*, 2007, Thompson *et al.*, 2012). Although these studies did not include neutral face expressions in FER paradigms or an examination of facial emotion misperceptions.

However, one study reported that the observed FER impairment among UHR individuals relative to healthy individuals was of a similar magnitude to that reported for individuals with schizophrenia and FEP (Addington *et al.*, 2008). More recent studies reported evidence for a specific impairment in the recognition of fearful and sad facial emotional expressions (Amminger *et al.*, 2012) and neutral face expressions (Van Rijin *et al.*, 2011). The latter study also examined facial emotion misperceptions and observed that neutral faces were more likely to be described as angry. The misperception of emotion in faces may represent one cognitive mechanism contributing to the social impairment that characterises UHR individuals. Consistent with this, a functional imaging study of individuals meeting UHR criteria revealed hyperactivation of the amygdala during the processing of neutral face expressions, which could reflect emotional salience being assigned to neutral stimuli (Seiferth *et al.*, 2008).

Only one study has examined differences in FER among UHR individuals who did and did not convert to psychosis. Results indicated that although UHR individuals exhibited an overall impairment in FER relative to healthy individuals, no differences in FER were observed between UHR individuals who converted to psychosis compared to those who did not at two-year follow-up (Addington *et al.*, 2012). Although Addington et al failed to examine differences between groups on specific emotions and facial emotion misperceptions the findings tentatively suggest that impairments in FER do not appear to be a risk marker for transition to psychosis within 24 months of meeting UHR criteria.

8.2.3 Children reporting psychotic like-experiences

To date, only three studies have examined FER among youth experiencing PLEs (Pelletier *et al.*, 2013, Roddy *et al.*, 2012, Thompson *et al.*, 2011b). A brief summary of each of these studies is provided in Table 19. Evidence indicates that poor FER at age 8 years was not associated with PLEs at 12 years (Thompson *et al.*, 2011b). However, between the ages of 10-13 years, adolescents reporting PLEs at clinical interview were impaired on FER primarily due to the poor recognition of sad facial emotion expressions (Roddy *et al.*, 2012). By contrast, young adults reporting high levels of non-clinical psychosis (NCP) performed significantly more poorly at recognising fearful facial emotion expressions only compared to those experiencing low levels of NCP (Pelletier *et al.*, 2013).

Though PLEs in childhood are significantly associated with later psychotic illness (Fisher *et al.*, in press, Poulton *et al.*, 2000, Welham *et al.*, 2009b), they are also associated with an increased risk of anxiety disorders (Poulton *et al.*, 2000) and other psychiatric disorders including affective disorders, drug use disorders, and personality disorders (Fisher *et al.*, in press, Werbeloff *et al.*, 2012), albeit to a lesser extent. Thus, PLEs constitute a relatively non-specific marker of risk for subsequent psychiatric disorders. Further, cross-sectional data from the general population indicate significant comorbidity of PLEs with emotional and behavioural problems (Barragan *et al.*, 2011, Kelleher *et al.*, 2012b). A recent systematic review of FER in children and adolescents found evidence for FER abnormalities across a wide range of mental disorders including mood disorders, anxiety disorders, eating disorders, conduct disorders, and attention deficit hyperactivity disorder (Collin *et al.*, 2013). Thus, the relationship between PLEs and FER observed by Roddy *et al* and Pelletier *et al* might reflect differences in the presence of unreported psychopathology.

8.2.4 Summary

Evidence of specific FER impairments in groups at-risk for schizophrenia is mixed. Variability in results could be explained by the differing characteristics of participants and/or FER paradigms (Edwards *et al.*, 2002). Consistent with this notion, studies using the Penn Emotion Recognition Test (ER40: Gur *et al.*, 2002) all reported FER impairments among at-risk youth relative to a comparison group (Eack *et al.*, 2010, Pelletier *et al.*, 2013, Roddy *et al.*, 2012), the three studies using the Diagnostic Analysis of Nonverbal Accuracy task (DANVA-2: Nowicki and Duke, 1994) observed no differences between at-risk and control groups (Davalos *et al.*, 2004, Thompson *et al.*, 2012, Thompson *et al.*, 2011b), inconsistent results were reported among at-risk studies (Addington *et al.*, 2008, Addington *et al.*, 2012, Li *et al.*, 2012, Meijer *et al.*, 2012, Pinkham *et al.*, 2007, Van Rijin *et al.*, 2011) using the Facial Emotion Identification and Discrimination (FEIT, FEDT; Kerr and Neale, 1993), and the Facial Affect Labelling Task (Van 'T Wout *et al.*, 2004). These findings indicate that the ER40 task may a more sensitive measure of FER among at-risk groups. Alternatively, abnormalties in FER among at-risk individuals may only be apparent when FER skills are fully developed (Herba *et al.*, 2006).

Overall, FER impairments are apparent not only among individuals with chronic schizophrenia (Kohler *et al.*, 2010) but also, among individuals experiencing FEP (Addington *et al.*, 2008, Thompson *et al.*, 2012), unaffected adolescent (though only for neutral facial expressions), and to some extent among adult first-degree relatives of individuals with schizophrenia (Bediou *et al.*, 2007, Eack *et al.*, 2010). Thus, specific abnormalities in FER may be present not only at illness onset, but could also index vulnerability for schizophrenia. Prospective studies following individuals at elevated risk for developing schizophrenia are needed to determine the extent to which impairments of FER precede illness and represent potential targets for early

intervention. In particular, more research is needed among different at-risk groups with a widely used FER paradigm incorporating more subtle displays of facial emotion expressions and investigating the nature of facial emotion misperceptions.

Table 19. Studies examining facial emotion processing

Study	Sample	Mean Age	Measure	Results	Effect size (Cohens *d*)
Individuals with a positive family history of schizophrenia or SSD					
Bolte and Poustka (2003)	11 siblings of individuals with schizophrenia (Sz-S), 22 healthy comparison individuals (Comp), 21 individuals with schizophrenia (Sz)	Sz-S (16 yrs), Comp (29 yrs), Sz (18 yrs)	The Facial Affect Recognition Test (happy, sad, fearful, disgust, anger, surprise, and neutral facial emotion expressions)[24]	No differences between Sz and Sz-S relative to Comp	
Davalos *et al*., (2004)	51 offspring of a parent with schizophrenia (Sz-O) and 51 Comp	Sz-O (10 yrs) / Comp (10 yrs)	DANVA-2[25]	No differences between Sz-O and Comp	
Eack *et al*., (2008)	70 Sz-O and 63 Comp	Sz-O (16 yrs) / Comp (16 yrs)	ER40 task (happy, sad, angry, fearful and neutral face emotion expressions)[26]	No significant differences overall but Sz-O significantly over-attributed emotions to neutral faces (primarily misattributing neutral faces as sad)	Neutral faces: *d*=-0.42

[24] The Facial Affect Recognition Test (Bormann *et al*., 1995)

[25] Adult version of the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2; Nowicki and Duke, 1994)

[26] The Penn Facial Emotion Recognition Task (ER40; Gur *et al*., 2002)

Study	Sample	Mean Age	Measure	Results	Effect size (Cohens *d*)
Barbour *et al*., (2010)	19 Sz-O and 25 Comp	Sz-O (14 yrs) / Comp (14 yrs)	Self-designed Emotion Recognition Task (happy, angry, sad, fearful, and neutral facial emotion expressions)	No significant differences between groups	
De Archaval *et al.*, (2010)	14 Sz-S, 14 Comp, and 14 Sz	Sz-S (30 yrs) / Comp (28 yrs) / Sz (30 yrs)	Self-designed Basic Emotion Labelling Task	Sz but not Sz-S significantly less accurate than Comp	
Li *et al.*, (2010)	23 Sz-S, 67 Comp, 69 Sz	Sz-S (30 yrs) / Comp (26 yrs) / Sz (26 yrs)	FEIT and FEDT (happy, angry, afraid, sad, surprised, and ashamed facial emotion expressions)[27]	Sz significantly impaired relative to Sz-S and Comp but Sz-S not impaired compared to Comp	
Li *et al.*, (2012)	12 Sz-S, 12 Comp, 12 Sz	Sz-S (30 yrs) / Comp (29 yrs) / Sz (29 yrs)	Self-designed Emotion Recognition Task (happy, fearful and neutral facial emotion expressions)	Sz significantly worse at identifying fearful faces compared to Comp but no differences between Sz-S and Comp	
Meijer *et al.*, (2012)	1044 Sz-S, 587 Comp, and 1093 Sz	Sz-S (27 yrs) / Comp (30 yrs) / Sz (54 yrs)	The Facial Affect Labelling Task[28]	Sz significantly worse on all emotions (except to happy) compared to Comp but differences between Sz-S and Comp	

[27] Facial Emotion Identification and Discrimination Tasks (FEIT, FEDT: Kerr and Neale, 1993)

[28]The Facial Effect Labelling Test (van't Wout, 2004)

Study	Sample	Mean Age	Measure	Results	Effect size (Cohens *d*)
Individuals meeting Ultra High-Risk criteria					
Pinkham *et al*., (2007)	19 Ultra High-Risk (UHR), 21 Comp, 21 first – episode psychosis patients (FEP), and 28 (Sz)	UHR (21 yrs) / Comp (27 yrs) / FEP (24 yrs) / Sz (39 yrs)	FEIT and FEDT (happy, angry, afraid, sad, surprised, and ashamed facial emotion expressions)[29]	UHR group not significantly different to Comp group but FEP and Sz groups significantly different to Comp but not each other	
Addington *et al.*, 2008	86 UHR, 55 Comp, 50 FEP patients, and 53 Sz	UHR (19 yrs) / Comp (21 yrs) / FEP (25 yrs), Sz (35 yrs)	FEIT and FEDT (happy, angry, afraid, sad, surprised, and ashamed facial emotion expressions)[28]	FEIT:UHR group significantly worse than Comp but similar to FE and Sz FEDT: Only Sz and FE significantly different to Comp	FEIT: *d*=-0.76
Seiferth *et al*., (2008)	12 UHR cases and 12 Comp	24 yrs	Self-designed task (happy, sad, angry, fearful and neutral facial emotion expressions)	No differences between groups	
Amminger *et al*., (2011)	79 UHR, 30 Comp, and 30 FEP	UHR (16 yrs) / Comp (15 yrs) / FEP (16 yrs)	Facial Affect Recognition task (sad, fearful, angry, surprise, and neutral facial emotion expressions)[30]	Significant differences between FE and UHR relative to Comp for fear and sad face emotions only.	Insufficient data to calculate effect size

[29] Facial Emotion Identification and Discrimination Tasks (FEIT, FEDT: Kerr and Neale, 1993)

[30] The Facial Affect Recognition Task (Edwards *et al*., 2001)

Study	Sample	Mean Age	Measure	Results	Effect size (Cohens *d*)
Gee *et al.*, (2011)	20 UHR and 14 Comp	UHR (18 yrs) / Comp (18 yrs)	Facial emotion labelling and matching task (happy, fearful, angry, and surprised facial emotion expressions)[31]	No differences between groups	
Van Rijin *et al.*, (2011)	36 UHR and 21 Comp	UHR (15 yrs), Comp (15 yrs)	The Facial Affect Labelling Test (angry, happy , fearful, and neutral)[32]	UHR group significantly worse than controls due to more errors in labelling neutral expressions with UHR making significantly more 'neutral-to-angry' misattributions	Neutral: *d*= -0.80
Thompson *et al.*, (2012)	30 UHR, 30 Comp, and 30 FEP patients	UHR (19 yrs), Comp (19 yrs), FEP (20 yrs).	DANVA-2 (happy, sad, fearful, and angry facial emotion expressions)[33]	FEP but not UHR significantly impaired relative to Comp	

[31] The Facial Emotion Labelling and Matching Task (Lieberman *et al.*, 2007)

[32] The Facial Effect Labelling Test (van't Wout, 2004)

[33] Adult version of the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2; Nowicki and Duke, 1994)

Study	Sample	Mean Age	Measure	Results	Effect size (Cohens *d*)
Children/Adolescents reporting psychotic like-experiences					
Thompson *et al.,* (2011)	6,455 members of British birth cohort (Avon Longitudinal Study of Parents and Children: ALSPAC)	Facial emotion processing assessment at 8 yrs. PLEs assessed in clinical interview at 12 yrs	DANVA-2 (happy, sad, fearful, and angry facial emotion expressions)	No association between facial emotion recognition at 8 yrs and definite PLEs and 12 years	
Roddy *et al.,* (2012)	793 adolescents recruited from a community-based screening programme in Ireland	10-13 years	ER40 (non-computerised version)[34]	Children who reported PLEs performed significantly more poorly primarily due to difficulties identifying sad faces	Insufficient data calculate effect sizes
Pelletier *et al.,(*2012)	35 individuals reporting high levels (top 10th percentile) of Non-Clinical Psychosis (NCP), 30 individuals with low levels of NCP (lowest 10th percentile)[35]	High-NCP (19 yrs) / low-NCP (19 yrs)	ER40[33]	High NCP borderline difference for overall accuracy and significantly different for fear facial emotion expressions relative to low NCP	Total accuracy: *d*=-0.40 Fear: *d*=-0.46

[34] The Penn Facial Emotion Recognition Task (ER40; Gur et al, 2002)

[35] Non-Clinical Psychosis assessed using the Launay-Slade Hallucination Scale (LSHS: Bentall and Slade, 1985).

Chapter 9 Misperceptions of facial emotions among youth aged 9-14 years who present multiple antecedents of schizophrenia

9.1 Aims of chapter

The present study sought to determine whether ASz children present FER difficulties similar to those reported among individuals with schizophrenia and at-risk youth, after accounting for IQ differences between ASz and TD groups (Cullen *et al.*, 2010) which may contribute to FER performance. The study examined overall performance on FER tasks, as well as the specific nature of facial emotion misperceptions. We hypothesized that ASz children would be less accurate than TD children in identifying emotions in facial expressions, and that they would more often mislabel neutral faces with other emotion expressions. In particular, we anticipated that ASz children would misidentify neutral expressions as sad, as was reported in a study of youth with family histories of schizophrenia using the same FER task (Eack *et al.*, 2010).

9.2 Method

9.2.1 Participants

Classrooms of children aged 9-14 years and their caregivers completed questionnaires to assess replicated antecedents of schizophrenia. In brief, ASz children were defined as those presenting: (1) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (Goodman, 2001); (2) a child-reported “certainly-true” response on at least one of nine PLE items assessing subclinical hallucination and delusion symptoms (Laurens *et al.*, 2012,

Laurens *et al.*, 2007); and (3) a caregiver-report of a motor and/or speech delay and/or abnormality. TD children were defined as those meeting none of these three criteria and who, in addition, had no first-, second-, or third-degree relative with schizophrenia or a schizophrenia spectrum disorder, as assessed by the FIGS interview (Maxwell, 1992) conducted with the child's caregiver.

The sample included 34 ASz and 34 TD participants, the latter selected as the best individual matches to the ASz children on sex, and ethnicity from among 44 TD children who completed the FER task. Five ASz children in the present study had at least one second-degree relative with a family history of schizophrenia or a schizophrenia spectrum disorder. None of the children presented a diagnosis of autism or Asperger's disorder, neurological disorder, learning difficulties (IQ<70), nor had ever taken antipsychotic medication. As presented in Table 20, at the time of testing, ASz and TD children did not differ on age, proportion male, ethnicity, or length of time since initial assessment. ASz children were characterised by significantly lower IQ than TD children.

Children provided written assent, and caregivers provided written informed consent, for participation in the study. Ethical review of the study was provided by the Joint South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry Research Ethics Committee.

Table 20. Demographic and Intellectual Characteristics of Participants on the Penn Emotion Recognition Task

	ASz (n=34)		TD (n=34)		Statistics
	n	(%)	n	(%)	
Proportion male	23	(68)	20	(59)	X^2 =0.6, df=1, p=0.5
Ethnicity [a]					X^2 =3.5, df=3, p=0.3
White British	9	(27)	12	(35)	
White other	7	(19)	11	(32)	
Black African; African-Caribbean	9	(27)	7	(21)	
Other	9	(27)	4	(12)	
	Mean	SD	Mean	SD	
Age at facial emotion assessment	12 y, 1 m	17 m	12 y, 5 m	16 m	$t_{(66)}$=-1.2, p=0.2
Mean time between completion of antecedent screening questionnaires and facial emotion assessment	23 m	14 m	28 m	14 m	$t_{(66)}$=-1.5, p=0.1
IQ [b]	98.6	10.3	109.7	12.2	$t_{(66)}$=-4.1, p<0.001

Notes: ASz: presenting the triad of antecedents of schizophrenia; TD: presenting none of antecedents of schizophrenia or family history of the disorder; y: years; m: months; [a] Ethnicity was assessed according to the UK Census ethnic categories defined by the Office of National Statistics 2001 (Laurens *et al.*, 2008); "Black African; African-Caribbean" included children of mixed white-Black African/Caribbean ethnicity; "Other" included children predominantly of mixed ethnicity; and [b] IQ estimated using Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999).

9.2.2 Measures

Facial emotion processing. FER was assessed using the Penn Emotion Recognition Task (ER40), a computerised task that requires participants to correctly recognise facial emotions. The ER40 has been used previously to study adults with chronic schizophrenia (Pinkham *et al.*, 2011), youth with a family history of schizophrenia or spectrum disorders (Eack *et al.*, 2010), adolescents reporting PLEs (Roddy *et al.*, 2012) and, more recently, young adults experiencing high and low levels of non-clinical psychosis (Pelletier *et al.*, 2013). The ER40 comprises 40 colour photographs of faces displaying happy, sad, angry, fearful, and neutral facial expressions (8 photographs of each emotional expression). The photographs were balanced for the intensity of emotion expressed (mild or high), and the age, gender, and ethnicity of the faces. Each face was presented serially on a computer screen, in random order, with five response options displayed to the right of each photograph (i.e., “happy”, “sad”, “angry”, “fear”, or “no emotion” [neutral]). For each photograph, participants were instructed to select the response that best described the displayed emotion, as quickly and as accurately as possible. Responses were selected by computer-mouse click. Each face was displayed until a response was recorded. Details of task construction and ratings have been reported previously (Gur *et al.*, 2002).

Dependent variables extracted from the task for analysis were: (1) number of correct responses for each type of emotion expression; and (2) number of misattribution and mislabelling responses made for each type of emotion.

9.2.3 Procedure

Eligible children and their primary caregivers were invited to participate in a research study in which children completed the ER40 task as part of a comprehensive

battery of assessments including measures of biological, psychosocial, and neurocognitive functioning. The ER40 was administered by a trained researcher using standard instructions. Participants practiced the task to ensure understanding of instructions. Testing time was approximately 10 minutes.

9.2.4 Statistical Analyses

Comparisons of the ASz and TD children on age at time of FER assessment, time since initial assessment and group assignment, and IQ, assessed using the two subtest version of the WASI (Wechsler, 1999), were made using independent t-tests; group differences on sex and ethnicity were tested using chi-square analyses. IQ was entered as a covariate in all FER analyses.

Previous investigations have indicated that FER performance improves during childhood and adolescence (Herba *et al.*, 2006). Accordingly, we performed correlation analyses between each ER40 variable and age; parametric correlation analyses (Pearson coefficient) were conducted on normally-distributed performance variables, and non-parametric correlation analyses (Spearman coefficient) were performed on non-normally distributed performance variables. No significant associations between task performance variables and age were detected.

9.2.4.1 Correct identification of facial emotions.

To examine the accuracy of facial emotion expression identification, a two group (ASz, TD) by five emotions (happy, sad, angry, fearful, neutral) repeated-measures ANCOVA adjusting for IQ was conducted on the number of correct responses recorded for each emotion.

9.2.4.2 Facial emotion misperceptions.

Facial emotion misperceptions were examined by summing the total number of responses that: (1) misattributed each emotion (e.g. sadness) to faces expressing another

emotion (e.g., misattributing happy expressions-*as*-sad, angry expressions-*as*-sad, fearful expressions-*as*-sad, and neutral expressions-*as*-sad error types); and (2) incorrectly labelled each emotion (e.g., mislabelling angry-*as*-happy expressions, angry-*as*-sad expressions, angry-*as*-fearful expressions, and angry-*as*-neutral expressions). For each of these ten variables, proportions of total misperceptions were created by dividing these sums by the total number of incorrect responses possible (i.e., 32), and multiplying by 100 to obtain a percentage for each misattribution and mislabelling misperception response type. Group differences were then explored using independent samples t-tests for normally distributed proportions or Mann-Whitney U tests for non-normally distributed proportions. Significant group effects were then further examined using repeated measures ANCOVAs on the mean number of misattribution or mislabelling responses, with IQ as a covariate. The mean number of misattributions and mislabelling responses were not normally distributed and a square root transformation was applied (Yamamura, 1999).

For all ANCOVAs follow-up simple main effects testing with Bonferroni adjustments for multiple comparisons were also conducted. Greenhouse-Geisser correction for repeated measures was employed for all but the mislabelling of emotions to face displaying anger, and with estimates of effect size for each analysis reported.

9.2.4.3 Assessment of triad stability.

FER assessments were completed, on average, two years after the initial identification of children using antecedent screening questionnaires. At the time of FER assessments, children completed the same questionnaires used to determine group assignments in order to re-assess the two ASz triad components that could change over time. Of the 34 ASz children, 4 (12%) obtained scores on the SDQ psychopathology subscales in the “normal” range based on UK population norms and they responded

"not true" on all nine PLE items. All ANCOVAS were repeated excluding these four children.

The numbers of misattribution and mislabelling responses were not normally distributed and a square root transformation was applied. Greenhouse-Geisser correction for repeated measures was employed for all but the misattribution of no emotion to faces displaying emotion and for the mislabelling of emotions to expressions of anger.

9.2.4.4 Associations with ASz components.

Four multiple linear regression models were computed to explore associations of the components of the antecedent triad with the four facial emotion processing outcome variables on which the full sample of ASz children performed significantly more poorly than TD peers: total correct facial emotion identifications, misattribution of neutral expressions to faces displaying other emotions, mislabelling of other emotions to faces displaying anger, and mislabelling of sadness to faces displaying neutral expressions. Each model included the six predictors assessing the triad components, total PLE score, total number of speech and/or motor delays or abnormalities, and scores for SDQ subscales assessing emotional problems, conduct problems, hyperactivity-inattention, and peer relationships problems.

9.3 Results

Table 21 presents means and standard deviations for correct responses by emotion type and for the four total emotion misperceptions (misattribution and mislabelling error) that showed statistically significant group differences. Cohen's *d* effect sizes indicating the magnitude of difference between groups (where an effect size of 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect; Cohen, 1992) and Bonferroni adjusted p-values are also indicated. Figure 20 illustrates the proportions of

misidentifications of each emotion to faces displaying no emotion, separately for ASz and TD children.

9.3.1 Correct identification of facial emotions

The two group (ASz, TD) by five facial emotion type (happy, sad, angry, fearful, neutral) ANCOVA on the number of correct responses, including IQ as a covariate, indicated a significant main effect of group [$F(1,65)=8.5$, $p=0.005$, $\eta p^2 = 0.12$], with TD correctly identifying more emotions than ASz . No significant main effect of emotion type [$F(3.1, 204.3)=2.1$, $p=0.09$, $\eta p^2 = 0.03$] or group-by-emotion interaction was detected [$F(3.1, 204.3)=2.0$, $p=0.11$, $\eta p^2 = 0.03$].

Table 21. Comparisons of performance on the ER40 Facial Emotion Recognition Task by ASz and TD Children

Performance variable (maximum score possible)	**ASz (n=34)**		**TD (n=34)**		**Effect size**
	M	**SD**	**M**	**SD**	**[b] p-value; Cohen's d**
Mean number of total correct responses (40)	30.2	3.7	33.1	2.4	<0.01; 0.9
Mean number of correct responses:					
Happy expressions (8)	7.8	0.5	7.9	0.4	0.37; 0.2
Sad expressions (8)	5.3	1.7	6.1	1.3	0.05; 0.5
Angry expressions (8)	4.0	1.6	4.9	1.1	0.02; 0.7
Fear expressions (8)	6.7	1.3	7.1	1.2	0.81; 0.3
Neutral expressions (8)	6.4	1.9	7.2	1.2	0.15; 0.3
Mean number of misperceptions[a]:					
Other emotions misattributed as "Sad" expressions	2.5	2.3	1.4	1.5	0.11; 0.6
Other emotions misattributed as "Neutral" expressions	3.9	2.2	2.5	1.4	<0.01; 0.8
"Angry" expressions mislabelled as other emotions	4.0	1.6	3.0	1.1	0.01; 0.7
"Neutral" expressions mislabelled as other emotions	1.7	1.9	0.8	1.2	0.14; 0.6

Notes: [a]Face emotion misperceptions repeated-measures ANCOVAs were performed on square root transformed data; and [b]p-values are for adjusted for IQ with Bonferroni corrections for multiple comparisons applied.

9.3.2 Facial emotion misperceptions.

Among the ten analyses conducted on the proportion of emotion misperception response types, four significant differences between ASz and TD were detected: (1) misattribution of sadness to faces displaying other emotion (z=-1.9, p=0.05); (2) misattribution of neutral expressions to faces displaying other emotions; (z=-2.7, p=0.007); (3) mislabelling other emotions to faces displaying angry expressions (z=-2.6, p=0.01); and (4) mislabelling other emotions to faces displaying neutral expressions (z=-2.2, p=0.02).

9.3.2.1 Misattribution of sadness to faces displaying other emotion

A two group (ASz, TD) by four facial expressions misattribution type (happy-as-sad, angry-as-sad, fear-as-sad, neutral-as-sad) repeated-measures ANCOVA, including IQ as a covariate, indicated no main effect of group [$F(1,65)=2.6$, $p=0.11$, $\eta p^2 = 0.04$], no main effect of misattribution type [$F(2.1,136)=0.63$, $p=0.54$, $\eta p^2 = 0.01$] and no group-by-misattribution type interaction [$F(2.1, 136)=2.4$, $p=0.09$, $\eta p^2 = 0.04$].

9.3.2.2 Misattribution of neutral expressions to faces displaying other emotions

A two group (ASz, TD) by four facial expression misattribution type (happy-as-neutral, sad-as-neutral, angry-as-neutral, fear-as-neutral) repeated-measures ANCOVA, including IQ as a covariate, indicated a significant main effect of group [$F(1,65)=7.6$, $p=0.007$, $\eta p^2 = 0.11$] due to ASz misattributing neutral expressions to faces displaying other emotions relative to TD (i.e., failing to detect emotion). No main effect of misattribution type [$F(2.8,185.5)=0.50$, $p=0.68$, $\eta p^2 = 0.008$] or group-by-misattribution type interaction was detected [$F(2.8, 185.5)=1.2$, $p=0.32$, $\eta p^2 = 0.02$].

9.3.2.3 Mislabelling of other emotions to faces displaying angry expressions

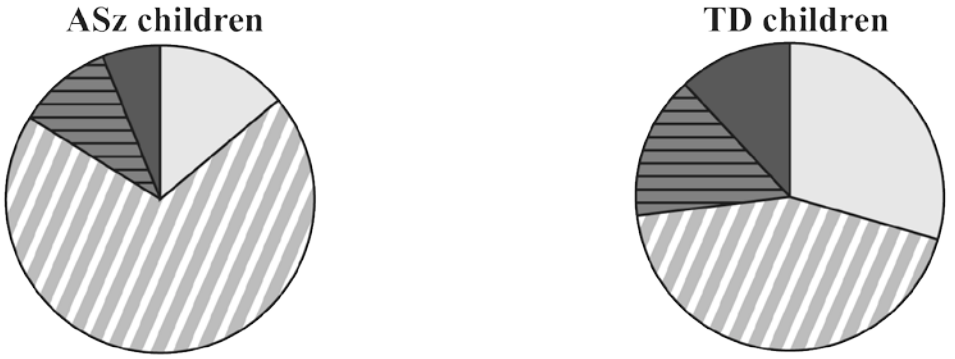
A two group (ASz, TD) by four mislabelling type (angry-as-happy, angry-as-sad, angry-as-ear, angry-as-neutral) repeated-measures ANCOVA including IQ as a

covariate, was computed. Results indicated a significant main effect of group [$F(1,65)=7.1$, $p=0.01$, $\eta p^2 = 0.1$], with ASz more often mislabelling angry expressions as displaying other emotions relative to the TD. No main effect of misattribution type [$F(3,195)=0.19$, $p=0.90$, $\eta p^2 =0.003$] or group-by-mislabelling type interaction was observed [$F3,195)=0.45$, $p=0.72$, $\eta p^2 =0.01$].

9.3.2.4 Mislabelling of emotion to faces displaying no emotion (neutral expressions)

A two-group (ASz, TD) by four mislabelling (neutral-as-happy, neutral-as-sad, neutral-as-fear, neutral-as-angry) repeated-measures ANCOVA, including IQ as a covariate, was conducted. Results indicated no main effect of group [$F(1,65)=2.2$, $p=0.14$, $\eta p^2 = 0.03$] or mislabelling type [$F(1.9,122.2)=0.12$, $p=0.88$, $\eta p^2 = 0.01$]. A significant group-by-mislabelling type interaction was detected [$F(1.9, 122.2)=3.2$, $p=.05$, $\eta p^2 = 0.05$], with ASz significantly more often mislabelling neutral expressions as sad than TD ($p=0.04$).

Figure 20. Proportions of other emotions mislabelled as neutral expressions



0.2 (14%)	Neutral-as-happy	0.2 (30%)
1.2 (70%)	Neutral-as-sad	0.4 (44%)
0.2 (10%)	Neutral-as-angry	0.1 (15%)
0.1 (6%)	Neutral-as-fear	0.1 (12%)
18%	Total percent for neutral	11%

9.3.3 Assessment of triad stability

ANCOVA's were repeated to examine FER differences among children who never met ASz criteria at either screening questionnaire or FER assessment (TD) compared to those ASz children who continued to experience multiple antecedents of schizophrenia at time of FER assessment after excluding four ASz cases who no longer reported SDQ psychopathology and/or PLEs.

9.3.3.1 Correct identification of facial emotions

Similar results were obtained after removing 4 ASz children from the analyses who no longer presented with threshold or subthreshold SDQ psychopathology or PLEs at time of FER assessment. The two group by five facial emotion type (happy, sad, angry, fearful, neutral) ANCOVA on the number of correct responses, including IQ as a covariate, indicated a significant main effect of group [$F(1,61)=6.5$, $p=0.01$, $\eta p^2 = 0.10$], with TD correctly identifying more emotions than ASz. No significant main effect of emotion type [$F(3.1, 189.7)=2.5$, $p=0.07$, $\eta p^2 = 0.04$] or group-by-emotion interaction was detected [$F(3.1, 189.7)=1.7$, $p=0.17$, $\eta p^2 = 0.03$].

9.3.3.2 Misattribution of sadness to faces displaying other emotions.

After removing 4 children from statistical analyses who no longer met ASz triad criteria at time of FER assessment, a two group by four facial expressions misattribution type (happy-as-sad, angry-as-sad, fear-as-sad, neutral-as-sad) repeated-measures ANCOVA, including IQ as a covariate, indicated a main effect of group [$F(1, 61)=4.1$, $p=0.05$, $\eta p^2 = 0.06$]; due to ASz significantly more often misattributing sadness to faces displaying other emotions, which was not apparent in results of full ASz sample. As before no main effect of misattribution type [$F(2.1, 127.9)=0.43$, $p=0.66$, $\eta p^2 = 0.01$] was observed but a trend group-by-misattribution type interaction [$F(2.1, 127.9)=2.9$, $p=0.07$, $\eta p^2 = 0.05$] was now reported.

9.3.3.3 Misattribution of neutral expressions to faces displaying other emotions.

Similar results were obtained after removing 4 ASz children from the analyses who no longer presented with concurrent SDQ threshold or subthreshold psychopathology or PLEs at time of FER assessment. The two group by four facial expression misattribution type (happy-as-neutral, sad-as-neutral, angry-as-neutral, fear-as-neutral) repeated-measures ANCOVA, including IQ as a covariate, indicated a significant main effect of group [$F(1, 61)=4.3$, $p=0.05$, $\eta p^2 = 0.06$]; due to ASz misattributing emotion in neutral expressions relative to TD (i.e., failing to detect emotion). No main effect of misattribution type [$F(3, 183)=0.72$, $p=0.53$, $\eta p^2 = 0.01$] or group-by-misattribution type interaction was detected [$F(3, 183)=1.0$, $p=0.39$, $\eta p^2 = 0.02$].

9.3.3.4 Mislabelling of other emotions to faces displaying angry expressions.

Similar findings were reported among ASz children who continued to display antecedents of schizophrenia at time of FER testing relative to TD children. A two group by four mislabelling type (angry-as-happy, angry-as-sad, angry-as-ear, angry-as-neutral) repeated-measures ANCOVA including, IQ as a covariate, indicated a significant main effect of group [$F(1, 61)=5.1$, $p=0.03$, $\eta p^2 = 0.08$], with ASz more often incorrectly labelling angry expressions as displaying other emotions relative to the TD. No main effect of mislabelling type [$F(3, 183)=0.15$, $p=0.93$, $\eta p^2 =0.002$] or group-by-mislabelling type interaction was observed [$F3, 183)=0.34$, $p=0.80$, $\eta p^2 =0.006$].

9.3.3.5 Mislabelling of emotion to faces displaying no emotion (neutral expressions)

No difference in results for the mislabelling of emotion to neutral expressions was observed among ASz children who continued to experience multiple antecedents of schizophrenia at time of FER assessment (excluding 4 cases who did not) relative to TD children after adjusting for IQ. A two-group by four mislabelling type (neutral-as-happy, neutral-as-sad, neutral-as-fear, neutral-as-angry) repeated-measures ANCOVA, indicated no main effect of group [$F(1, 61)=2.9$, $p=0.09$, $\eta p^2 = 0.05$] or mislabelling

type [F(1.9, 114.6)=0.03, p=0.96, ηp^2 = 0.01]. A significant group-by-mislabelling type interaction was detected [F(1.9, 114.6)=4.5, p=0.02, ηp^2 = 0.07], with ASz significantly more often mislabelling neutral expressions as sad than TD (p=0.02).

9.3.4 Associations with ASz components

From all four regression models, only one significant relationship was detected: hyperactivity-inattention problems independently predicted mislabelling of sadness to faces with neutral expressions (β=0.10, t=-2.2, p=0.04).

9.4 Discussion

This study of FER extends the findings from Chapters Six and Seven of the thesis and our recent work characterising dysfunctions among children presenting multiple, well replicated antecedents of schizophrenia (Cullen *et al.*, 2013, Cullen *et al.*, 2010, Cullen *et al.*, submitted, Laurens *et al.*, 2010, Macmanus *et al.*, 2012, Matheson *et al.*, 2013). At the initial assessment, these children were younger than youth examined in previous FER investigations who had a family history of schizophrenia or who met UHR criteria. As hypothesised, ASz children performed more poorly on FER than TD children after accounting for group differences in IQ. This finding is similar to that reported for older UHR samples (Addington *et al.*, 2008, Van Rijin *et al.*, 2011). These findings also extend previous observations of FER impairments among adults with schizophrenia (Kohler *et al.*, 2003), and individuals at-risk for schizophrenia, in some (Addington *et al.*, 2008, Eack *et al.*, 2010, Pelletier *et al.*, 2013, Roddy *et al.*, 2012, Van Rijin *et al.*, 2011) but not all studies (Amminger *et al.*, 2012, Pinkham *et al.*, 2007, Thompson *et al.*, 2012, Thompson *et al.*, 2011b). In addition, ASz children, as compared to TD children, misattributed faces displaying emotions as neutral expressions, and more often mislabelled neutral expressions as sad. Further, the examination of mislabelling of faces displaying anger indicated that ASz children had some difficulties identifying anger. Amongst ASz children, FER performance was not

associated with specific components of the antecedent triad, with the exception that the score for hyperactivity-inattention problems independently predicted misattribution of sadness to faces with neutral expressions. Previous studies have not reported specific biases in FER task performance among adolescents with Attention Deficit Hyperactivity Disorder, but indicate that these adolescents show random patterns of performance associated, perhaps, with impulsivity (Cadesky *et al.*, 2000). Thus, for the most part, the components of the triad of antecedents did not independently account for FER difficulties observed among ASz children. Rather, it was the combination of all of the antecedents defining ASz that was associated with anomalies in FER task performance.

ASz children had difficulty correctly identifying angry facial expressions relative to TD children. However, among adults with schizophrenia and individuals with first-episode psychosis, pronounced difficulties are apparent in recognising negative emotions such as anger, fear, and disgust (Kohler *et al.*, 2003, Premkumar *et al.*, 2008, Thompson *et al.*, 2012). An investigation of individuals who met UHR criteria, and who were approximately three years older than children in the present study, reported difficulties only in recognising fear and sadness (Amminger *et al.*, 2012). More recently, a study of youth 10-13 years who reported PLEs observed difficulties identifying sadness in faces using a pencil and paper version of the ER40 task (Roddy *et al.*, 2012). By contrast, a borderline statistically significant impairment in recognising fear was reported among young adults with high levels of non-clinical psychosis relative to those experiencing low levels, using the well-validated computerised version of the ER40 task (Pelletier *et al.*, 2013). Inconsistent evidence for an impairment in recognition of negative facial emotion expressions among at-risk individuals suggests that these difficulties may become more apparent when FER skills are fully developed (Herba *et al.*, 2006).

Alternatively, inconsistencies in results of FER impairments across high-risk samples may result from differences in methodologies, including task design, emotion expressions that are assessed, and stimulus complexity (Edwards *et al.*, 2002). In particular, the absence of neutral facial expressions in some FER paradigms is notable. Of the studies (Amminger *et al.*, 2012, Eack *et al.*, 2010, Pelletier *et al.*, 2013, Roddy *et al.*, 2012, Van Rijin *et al.*, 2011) that included neutral faces and reported differences in FER among individuals at high-risk for schizophrenia relative to a healthy comparison group, two reported a specific impairment in the recognition of neutral facial expressions among the high-risk participants (Eack *et al.*, 2010, Van Rijin *et al.*, 2011). The studies that detected no difference in FER performance between at-risk and healthy individuals did not include neutral facial expressions in their FER paradigms (Pinkham *et al.*, 2007, Thompson *et al.*, 2012, Thompson *et al.*, 2011b).

ASz children misattributed emotions to neutral expressions, and more often mislabelled a neutral expression as sad compared to healthy peers. It was not possible to explore potential interactions between emotion type and intensity of the expressions. Consequently, the present study could not determine whether the response bias shown by ASz children reflected problems identifying emotions of low intensity in faces. Previously reported hyper-activation of the amygdala during processing of neutral expressions may explain, at least in part, the mislabelling of emotions to neutral expressions by ASz children. And, as suggested in previous reports of similar findings (Eack *et al.*, 2010, Pinkham *et al.*, 2011, Seiferth *et al.*, 2008, Van Rijin *et al.*, 2011), this result from the present study is consistent with the notion that the development of schizophrenia involves the aberrant assignment of salience to insignificant stimuli (Kapur, 2003).

ASz children, by definition, present several of the known antecedents of schizophrenia including motor/speech abnormalities, PLEs, and social, emotional and/or

behavioural problems. Previous studies by our group have also shown that they present with dysfunctions characteristic of individuals with schizophrenia (Laurens *et al.*, 2011). The present study shows that these children also exhibit difficulty recognising emotions in the faces of others, thereby lacking crucial information needed to guide their own behaviour and to understand the behaviour of others. It is plausible that the misinterpretation of facial emotions may contribute to the initiation of and/or persistence of PLEs. Indeed, previous research has indicated that difficulties in accurately perceiving emotion in the faces of others, particularly the mislabelling of neutral faces as negative expressions, contributes to some symptoms of schizophrenia such as delusion formation and suspicious thoughts (Holt *et al.*, 2006). It was not possible to determine the precise temporal association between the onset of PLEs and poor FER in the present study. FER difficulties were observed; however, in these ASz children who continued to present the triad of antecedents of schizophrenia at time of FER assessment, approximately two years after the initial assessment. Thus, poor FER may be associated with persistent PLEs and social, emotional, and behavioural difficulties. Furthermore, difficulties with FER may also contribute to the poor social functioning observed among adults with schizophrenia (Marwick and Hall, 2008), to the declining social and role functioning that characterizes the prodromal period, and also to the premorbid social impairments reported among youth who subsequently develop schizophrenia (Welham *et al.*, 2009a). Recent work by our group, reported that ASz children aged 9-14 years are significantly more socially withdrawn than TD peers (Matheson *et al.*, 2013). Thus, interventions that have been shown to increase the accuracy of facial emotion recognition among adults with schizophrenia (Frommann *et al.*, 2003, Wolwer and Frommann, 2011) could potentially benefit ASz children.

9.4.1 Strengths and Limitations

The present study has several limitations. The ER40 task output did not distinguish correct emotion responses by the two levels of emotional intensity displayed in the faces. Therefore, it is not clear whether the significant differences between ASz and TD children in mislabelling a neutral expression as sad or incorrectly identifying emotional expressions as neutral or sad occurred primarily in facial expressions of low intensity. In real life social interactions, faces typically display subtle variations in emotional expressions. Further, FER difficulties observed among ASz children may also be due to basic face identification/perception deficits that were not examined. Deficits in face perception have been identified in some, but not all, studies of adults with schizophrenia (Marwick and Hall, 2008), and may reflect impairments in memory and attention (Hooker and Park, 2002, Whittaker *et al.*, 2001). To date, only one study has included a task of face perception while investigating FER deficits among individuals at-risk for schizophrenia, and findings indicated no impairment (Van Rijin *et al.*, 2011). Finally, the present study was limited by a relatively small sample. Nonetheless, despite limited statistical power, the results consistently demonstrated that children who presented multiple antecedents of schizophrenia since late childhood presented FER difficulties compared to TD peers.

The current study benefited from using a FER test that has been used widely in previous studies of schizophrenia, and, importantly, incorporated neutral facial expressions. This allowed for meaningful comparisons of results with some previous studies (Eack *et al.*, 2010, Kohler *et al.*, 2003, Pelletier *et al.*, 2013, Pinkham *et al.*, 2011). The study identified children characterised by multiple, well replicated antecedents of schizophrenia. This strategy may capture a broader range of children at-risk for schizophrenia than selecting children with a family history of illness, and a smaller number with higher risk than studies using only one antecedent such as PLEs to

select children. Only follow-up of children defined as presenting ASz will determine the specificity and sensitivity of the present strategy for identifying children who will subsequently develop schizophrenia.

9.4.2 Conclusions

The present study obtained evidence of impairments in FER abilities among children and adolescents who may be at elevated risk for developing schizophrenia in adulthood. The study provided further support for the accumulating evidence that misattributions of emotional facial expressions as neutral, and the identification of neutral expressions as sad, may represent early risk markers for later development of schizophrenia. These impairments may represent targets for preventive interventions, which may in turn facilitate generalised improvements in social and emotional functioning among individuals at-risk for schizophrenia.

Chapter 10 Discussion

Aims of chapter

The aim of the thesis was to assess the utility of a novel identification strategy for identifying children aged between 9 and 12 years at-risk of developing schizophrenia or SSD. The CHADS project used questionnaires completed by children and caregivers to assess a triad of well-replicated antecedents of schizophrenia (Laurens *et al.*, 2007, Laurens *et al.*, 2011). Studies included in the thesis investigated whether children identified using this novel screening approach were characterised by cognitive and facial emotion processing abnormalities that were qualitatively similar to those observed among adults with schizophrenia and among youth at elevated risk for schizophrenia or SSD based on existing early identification approaches outlined in Chapter One. This final chapter presents an overview of the findings and discusses the implications.

10.1 Summary of results

The first study of the thesis (Chapter Four) employed meta-analytic techniques to examine whether low IQ, poor motor function, and scholastic under-achievement characterised children and adolescents who subsequently developed schizophrenia or SSD in adulthood. Consistent with previous meta-analyses that included assessments of older individuals and symptomatic, help-seeking youth meeting UHR criteria (Khandaker *et al.*, 2011, Woodberry *et al.*, 2008), results indicated a significantly lower IQ among individuals who developed schizophrenia or SSD in adulthood. Therefore, the findings from the meta-analysis extend previous work by confirming that this IQ deficit is present in early to mid-adolescence. The results of the meta-analyses examining cognitive function among children and adolescents who subsequently developed schizophrenia or SSD in adulthood, also contribute new knowledge by showing that, by age 16, individuals who develop schizophrenia or SSD in adulthood

displayed poorer motor function than peers who remained healthy. Thus, low IQ and motor deficits, but not poor scholastic achievement, precedes the onset of illness and the prodrome.

Chapter Six was a cross-sectional study of cognitive function among ASz, FHx^{H}, FHx^{L}, and TD children aged 9 to 12 years. Results indicated that compared to TD children, ASz and FHx^{H} children exhibited significantly poorer verbal IQ, scholastic achievement, and verbal working memory, indicating that these impairments are common to two groups of children defined in different ways to be at risk for schizophrenia or SSD. FHx^{H} children additionally displayed significantly lower full-scale IQ, verbal memory, and executive function impairments. Relative to TD children, FHx^{L} children showed no differences in cognitive performance. Thus, by the end of childhood, cognitive impairments were observed among two groups of children at risk for schizophrenia and SSD. Results were consistent with several reviews of cognitive functioning among adults with schizophrenia and among adolescents and young adults with a positive family history of schizophrenia or SSD (Agnew-Blais and Seidman, 2013, Erlenmeyer-Kimling, 2000, Mesholam-Gately *et al.*, 2009, Niemi *et al.*, 2003, Reichenberg and Harvey, 2007).

The results of the study of cognitive function among children aged 9 to 12 years also showed that, after the inclusion of full-scale IQ as a covariate in analyses, group differences in performance in specific neurocognitive domains were attenuated, suggesting that specific cognitive impairments among FHx^{H} and ASz children may reflect, at least in part, IQ differences between groups. This is consistent with evidence from the meta-analyses described in Chapter Four which demonstrated that lower than average premorbid IQ characterises children and adolescents who subsequently develop schizophrenia. The findings from the study of cognitive function among ASz, FHx^{H}, FHx^{L}, and TD children was also in line with existing work indicating greater

neurocognitive impairment among youth with first-degree as compared to those with a second-degree relative with schizophrenia before the typical age of risk for onset (Keshavan *et al.*, 2010).

The literature review of cognitive function among youth at elevated risk for the development of schizophrenia (Chapter Five) highlighted the relative paucity of longitudinal studies examining the developmental course of cognitive functions prior to the age typically associated with the onset of prodromal symptoms among children at-risk for schizophrenia or SSD. It had not previously been established whether different definitions of risk identified children presenting distinct developmental patterns of cognitive impairments. The longitudinal study of cognitive function in Chapter Seven contributed new knowledge on the development of cognitive functions by investigating age-related stability and change in multiple cognitive domains based on repeated assessments spanning childhood and into adolescence among FHx and ASz children compared to TD peers.

The results of this chapter, when unadjusted for ethnicity and parent's occupation, indicated that ASz and FHx youth, relative to TD youth, presented impairments in scholastic achievement (word reading and numerical operations measures) and verbal working memory from age 9 to 15 years. In addition, ASz children were also characterised by lower IQ, poorer performance on spelling (scholastic achievement domain) and the EF-category accuracy measure from age 9 to 15 years. FHx children showed a slower rate of improvement in spelling over time than the TD children. FHx youth also displayed initial increases in IQ and the EF-inhibition/switching measure relative to TD children, narrowing the observed gap between the two groups at age 11 years, but over time, this increase slowed and the differences between FHx and TD groups widened again. Both ASz and FHx children showed improvement in scores on measures of verbal memory and EF (category fluency, category accuracy, inhibition,

and inhibition/switching indices) obtaining scores similar to those achieved by the TD children by age 15 years. Thus, among children at risk for schizophrenia (i.e., those presenting with multiple antecedents of the disorder and those having affected relatives), cognitive development appears to differ across risk groups, measures, and periods of time. Further longitudinal follow-up is necessary to establish whether these differences in cognitive development will be associated with differences in risk for schizophrenia or SSD.

The final study in this thesis compared facial emotion processing among ASz and TD children. An established FER task (ER40) was used to assess correct recognition of happy, sad, angry, fearful, and neutral expressions, and misperceptions of these emotions. Relative to TD children, ASz children presented an overall impairment in facial emotion recognition. Further, ASz children misattributed neutral expressions to faces displaying other emotions, and also more often mislabeled a neutral expression as sad compared to healthy peers. The results were consistent with previous observations of FER impairments among adults with schizophrenia (Kohler *et al.*, 2003), and youth at elevated risk for schizophrenia or SSD, in some (Addington *et al.*, 2008, Eack *et al.*, 2010, Pelletier *et al.*, 2013, Roddy *et al.*, 2012, Van Rijin *et al.*, 2011) but not all studies (Amminger *et al.*, 2012, Pinkham *et al.*, 2007, Thompson *et al.*, 2012, Thompson *et al.*, 2011b). The results also provided further support for the accumulating evidence that misattributions of emotional facial expressions as neutral, and the identification of neutral expressions as sad, may represent early risk markers for later development of schizophrenia or SSD.

The hypotheses are restated in Table 22 along with a summary of results.

Table 22. Thesis hypotheses and results

Hypothesis	Supported?	Specific Results
Meta-analyses would show that cognitive and motor deficits would be present prior to the prodromal phase of schizophrenia among youth who subsequently develop schizophrenia in adulthood. (Chapter Four).	Partially supported	• IQ deficit observed at 16 years or younger and at 13 years or younger. • Motor deficit observed at 16 years or younger. • No differences in either overall scholastic achievement or on mathematics ability.
ASz, FHx^{H}, and FHx^{L}, children aged 9-12 years would be characterized by poorer cognitive performance in IQ, scholastic achievement, memory, and executive function relative to TD peers, but that the pattern of impairment might differ across the at-risk groups (Chapter Six)	Partially supported	• ASz and FHx^{H} children exhibited significantly poorer verbal IQ, scholastic achievement, and verbal working memory compared to TD children • FHx^{H} children additionally displayed significantly lower full-scale IQ, verbal memory, and EF impairments compared to TD children • Relative to TD children, FHx^{L} children showed no differences in performance on any cognitive domain.
Between 9-12 years, FHx^{H} children would display greater neurocognitive impairment than FHx^{L} children (Chapter Six)	Yes	• Greater neurocognitive impairment was observed on all measures except visual memory for FHx^{H} relative to FHx^{L} children.
Specific cognitive impairments observed at 9-12 years among ASz, FHx^{H}, and FHx^{L} children would reflect a lower generalised cognitive deficit (Chapter Six)	Partially supported	• Group differences on all neurocognitive domains were attenuated except for measures of visual memory and EF-inhibition/switching.
Between the ages of 9-15 years, FHx and ASz children would show different developmental trajectories in IQ, scholastic achievement, memory, working memory and	Yes	• ASz and FHx youth presented impairments in scholastic achievement (word reading and numerical operations measures) and verbal working memory from age 9 to 15

Hypothesis	Supported?	Specific Results
EF relative to TD children (Chapter Seven).		years compared to TD children. • ASz children were additionally characterised by lower IQ, poorer performance on spelling (scholastic achievement domain) and EF- category accuracy measure from age 9 to 15 years. • FHx group demonstrated a slower rate of improvement in spelling than the TD children. FHx youth experienced initial increases in IQ and on the EF-inhibition/switching measure relative to TD children, narrowing the observed gap between the two groups at age 11 years, but over time this relative increase slowed and differences between FHx and TD groups widened. • ASz and FHx children showed improvement in scores obtained on measures of verbal memory and EF (category fluency, category accuracy, inhibition, and inhibition/switching) to levels similar to those achieved by the TD children by age 15 years.[36]
ASz children would be less accurate than TD children in identifying emotions in facial expressions, and that they would more often mislabel neutral faces with other emotion expressions (Chapter Nine).	Yes	Relative to TD group: • ASz children were less accurate at recognising facial emotions. • ASz children more often misattributed faces displaying emotions as neutral expressions. • ASz children more often mislabelled angry faces with other emotions. • ASz children more often mislabelled neutral faces as sad

[36] After adjusting statistical models for ethnicity and parent's occupation only statistically significant stable deficits over time remained on IQ, scholastic achievement (word reading and numerical operations), and verbal working memory for ASz as compared to TD children.

10.2 Contribution of research to the understanding of child development

Research from this thesis has two main implications for child development. Firstly, during childhood and adolescence, cognitive development appears to be highly variable; characterised by periods of little change, rapid improvements in function, and for some measures, a decrease in rates of improvements (Elman, 2005, Waber *et al.*, 2012). In line with existing literature on the cognitive development of healthy children and adolescents, results of the longitudinal examination of cognitive function indicated that among TD children verbal memory scores had developed fully by 9 years of age. This study chapter also indicated that among TD children, EF abilities continued to develop throughout adolescence, consistent with the ongoing maturation of the frontal lobes during this period (Giedd *et al.*, 1999). Therefore, any conclusions drawn from the findings of this thesis must be interpreted within the context of continuities and discontinuities in the development of cognition among the TD children (Freedman and Brown, 2011). Indeed, understanding the developmental trajectory of the normal adolescent brain may be a prerequisite to understanding the aetiology of schizophrenia (Catts *et al.*, 2013).

Secondly, the study reported in Chapter Nine was among the first to examine the aberrant perceptions of facial emotions among children at elevated risk for schizophrenia. ASz children made significantly more misattributions of emotional facial expressions as neutral, identifying neutral expressions as sad, compared to TD children. Evidence indicates that conduct problems are associated with abnormal responses to fearful faces (Fairchild *et al.*, 2009), depressed children are more likely to perceive low-intensity expressions as sad (Schepman *et al.*, 2012), and adolescents with elevated trait anxiety were more likely to interpret ambiguous faces as angry (Richards *et al.*, 2007). An understanding of how facial emotion expressions are used to direct social interactions and inform appropriate social responses is crucial to informing us of the

extent to which specific biases may distinguish between types of childhood psychopathology.

10.3 Contribution of research to the understanding of the development of schizophrenia

Findings from the thesis indicate that, by age 16, individuals who subsequently develop schizophrenia or SSD displayed poorer motor function than those who remained healthy. Deficits in motor function have been reported to be among the first notable markers that identify children who develop schizophrenia (Fish, 1987, Walker *et al.*, 1994). Thus, the results of the meta-analyses in Chapter Four supports the inclusion of motor delays/abnormalities in screening questionnaires designed to identify children aged 9-12 years at elevated risk for the development of schizophrenia as this is one of strongest predictors of schizophrenia or SSD outcome. Importantly, although the findings of the meta-analyses cannot address whether a decline in cognitive function is apparent prior to or during the prodromal phase of schizophrenia, the presence of low IQ and poor motor function in childhood among individuals who later develop schizophrenia compared to those who do not does supports the notion that schizophrenia is, in part, a disorder of neurodevelopment.

The literature review of cognitive functions indicated that a wide range of cognitive impairments characterise relatives of individuals with schizophrenia aged 30 years or younger, UHR youth, and children/adolescents experiencing PLEs. However, groups identified using different definitions of risk exhibit contrasting patterns of cognitive impairment. Methodological inconsistencies across studies may account for these differences; however, based on the available evidence, it would appear that cognitive impairment is a risk marker for schizophrenia and SSD and may be associated with the disease process itself, though the exact nature and precise timing of these impairments have yet to be confirmed.

Cognitive impairments have been observed among adults with schizophrenia, individuals experiencing a first episode of psychosis, and individuals meeting UHR criteria (Matheson *et al.*, 2011). The impairments include specific deficits in memory, learning, executive function, attention, and processing speed that are evident against a background of generalised cognitive deficit, as indexed by measures of general intelligence (IQ) (Forbes *et al.*, 2006, Mesholam-Gately *et al.*, 2009, Reichenberg and Harvey, 2007). There is evidence that matching groups of adults with schizophrenia or individuals with FEP to healthy comparisons individuals on IQ does not account fully for the impairments observed in attention, processing speed, reasoning/problem solving, verbal memory, visual memory, working memory, and EF (Gray *et al.*, 2013, Leeson *et al.*, 2010).

The results outlined in Chapter Four indicated that, among individuals who develop schizophrenia in adulthood as compared to those who do not, an IQ deficit was shown to be present by 13 years. A recent meta-analyses of longitudinal population cohorts indicated that the lower the premorbid IQ the higher the risk for later schizophrenia (Khandaker *et al.*, 2011). Moreover, the same meta-analysis also observed that the larger the premorbid IQ deficit the earlier the onset of schizophrenia. The cross-sectional examination of cognitive function in the thesis, demonstrated significantly lower full-scale IQ among FHx^{H} children as compared to TD children, and lower verbal IQ (verbal comprehension) among ASz and FHx^{H} children compared to TD children. However, specific cognitive deficits observed among ASz and FHx^{H} were explained group differences in IQ relative to TD children. Liability for schizophrenia may be reflected, in part, by lower IQ.

The longitudinal analyses presented in Chapter Seven provided new evidence on the nature and timing of cognitive impairments among two groups of at-risk children. For the most part, among ASz and FHx children, deficits in IQ, scholastic achievement,

working memory, and executive function that were already present in childhood (9-12 years) remained stable into adolescence (up to 15 years). FHx children displayed a slower increase in spelling scores, whilst initial improvements in IQ and EF-inhibition/switching were followed by significant decreases in rates of improvement over time. The differences in rates of change of cognitive functions among youth at-risk for schizophrenia may indicate differing capacities for neural plasticity and targets for remediation (Maziade *et al.*, 2011a). Maziade and colleagues found that among offspring of parents with psychosis, visual memory impairments in childhood were predictive of psychosis, although subsequently this childhood impairment in visual memory improved with age to levels similar to that observed among a healthy comparison group (Maziade *et al.*, 2008, Maziade *et al.*, 2011b).

In line with models of neuroplasticity (Skibo and Nikonenko, 2010) and models of risk of cancer (Sherr, 2004), the authors proposed a model in which disturbed neurogenesis in some areas of the brain in FHx children would elicit a compensatory response proportional to the severity of the deficits (Maziade and Paccalet, 2013). The authors suggested that the improvement in scores obtained by the at-risk children could be due to a healthy protective gene, such that children who do not exhibit this catch-up would develop schizophrenia or SSD and have inherited the defective gene (Maziade and Paccalet, 2013). Indeed, results from the cross-sectional analyses of cognitive function of ASz, FHx^{H}, FHx^{L}, and TD children showed that FHx^{H} children demonstrated large effect size impairments in verbal memory and EF-category accuracy at 9 to 12 years relative to TD children. Relative to TD children, FHx children demonstrated significantly faster rates of improvement on these cognitive measures, with levels of performance reaching a similar level to TD children at 15 years.

ASz children examined in the cross-sectional and longitudinal studies of cognitive function in this thesis, to the best of our knowledge, did not present with a family

history of schizophrenia, but were instead characterised by a triad of antecedents of the disorder. However, ASz children also displayed a similar compensatory response over time as the FHx children. The longitudinal analyses of cognitive function described in Chapter Seven demonstrated that ASz children showed faster rates of improvement on measures of verbal memory and EF-Inhibition than TD children. Evidence from the cross-sectional analyses of cognitive function in this thesis and findings from a previous study of cognitive function among a smaller sample of ASz children indicated that these cognitive functions were among the most impaired compared to TD children at 9 to 12 years (Cullen *et al.*, 2010). Therefore, whilst results from this thesis demonstrated that verbal IQ, scholastic achievement, and verbal working memory may reflect risk for psychosis among both ASz and FHx^{H} children, the assessment of cognitive function at a single time point may be insufficient to identify children who may present an elevated risk for the development schizophrenia (Reichenberg *et al.*, 2010).

The literature review of facial emotion processing indicated that evidence for impairment in FER among relatives of individuals with schizophrenia aged 30 years or younger, youth meeting UHR criteria, and children/adolescents reporting PLEs is inconsistent. Again, this may reflect methodological differences across the studies. Therefore, it is not yet clear whether poor FER in general is a risk marker for the development of schizophrenia or SSD in adulthood. Performance on a FER test that has been used widely in previous studies of adults with schizophrenia indicated that ASz children were characterised by significantly more misattributions of emotional facial expressions as neutral, and the identification of neutral expressions as sad compared to TD children. The misattribution of negative emotions to neutral expressions has been previously observed among individuals with schizophrenia (Kohler *et al.*, 2003, Pinkham *et al.*, 2011, Premkumar *et al.*, 2008) and among youth at elevated risk for the

development of schizophrenia (Eack *et al.*, 2010, Van Rijin *et al.*, 2011) and suggests this type of misperception may represent an early risk marker schizophrenia.

Thus, ASz children exhibit difficulty recognising emotions in the faces of others, thereby lacking crucial information needed to guide their own behaviour and to understand the behaviour of others. The mislabelling of neutral stimuli may provoke a cascade of negative attributions resulting from negative social interactions (Pinkham *et al.*, 2011). Recent work has reported that ASz children aged 9-14 years were significantly more socially withdrawn than TD children (Matheson *et al.*, 2013). This may potentially increase vulnerability for depression, which is a common prodromal symptom of schizophrenia (Hafner *et al.*, 1995), and is associated with transition to psychosis among individuals meeting UHR criteria (Yung *et al.*, 2007a).

Previous investigations have shown that ASz children, compared to TD children, were characterised by features qualitatively similar to those observed among adults with schizophrenia including: (1) poorer performance on standardized intelligence and neuropsychological tests of executive function and memory (Cullen *et al.*, 2010); (2) elevated levels of social withdrawal (Matheson *et al.*, 2013); (3) dyskinetic movement abnormalities (Macmanus *et al.*, 2012); (4) reduction in the amplitude of the error-related negativity event-related potential component generated in the anterior cingulate that indexes internal monitoring of behaviour (Laurens *et al.*, 2010); (5) structural brain anomalies in the temporal lobe (Cullen *et al.*, 2013); and (6) experience of a greater number of, and sensitivity to, daily life stressors (Cullen *et al.*, submitted). Evidence also indicates that the prevalence of the ASz triad criteria is increased in a group in which the prevalence of schizophrenia is also elevated, that is, individuals of African-Caribbean and black African heritage in the UK (Laurens *et al.*, 2011, Laurens *et al.*, 2008). While only follow-up of ASz children will establish the extent to which the ASz criteria are predictive of schizophrenia and SSD, results from the study chapters

examining ASz children extend previous findings from the CHADS and provide further validity for the community screening tool designed to assess well-replicated antecedents of schizophrenia.

Further, the study reported in Chapter Seven observed changes in cognitive functions over time among the children who continued to meet ASz criteria at FU24 and FU48 follow-up assessments. An investigation of facial emotional processing (Chapter Nine) reported impaired FER abnormalities among ASz children after removing from the analyses those ASz children who no longer met ASz criteria of clinically significant psychopathology or PLEs at time of FER assessment. Importantly, only four children (approximately 12%) at FU24 and one child at FU48 (approximately 3%), included in Chapters Seven and Nine of this thesis no longer met ASz triad criteria. These findings indicate that the great majority of the children who met ASz criteria at the initial assessment continued to present these antecedents through the subsequent four years.

10.4 Implications of research for early intervention

Results of the studies reported in this thesis have implications for early intervention strategies. Interventions that treat individuals when early symptoms/abnormalities emerge could theoretically minimise further development of symptoms and associated biological damage, improve long-term treatment response, and even outcome (Yung and Mcgorry, 1996a). To date, early intervention efforts among UHR individuals in the prodromal phase have successfully delayed, but not averted, transition to psychosis (Yung *et al.*, 2007b). A review of treatment effectiveness among UHR studies, including antipsychotic medication, cognitive behavioural therapy, cognitive therapy, intensive community care programme with family psychoeduction, and omega-3 polyunsaturated fatty acid supplements, reported that at one year follow-up, all treatments were associated with lower risk of developing psychosis (Preti and Cella,

2010). Presently, there appears to be little evidence regarding efficacy of specific treatments of UHR individuals (Preti and Cella, 2010).

Growth in early intervention services based on the prodromal symptoms has led to an increase in the number of false-positive cases being referred to clinics. Further, concerns over the high number of false-positives, unnecessary exposure to treatment, and ethical considerations regarding the stigmatisation of individuals on an irreversible trajectory towards psychosis, has led to calls for early intervention approaches to focus on early mental distress based on a clinical staging model of psychopathology described in Chapter One of this thesis (Fusar-Poli *et al.*, 2013b).

Recognising and intervening with individuals at-risk for schizophrenia or SSD during the premorbid phase could prevent or minimise the underlying deviant development and the resulting disability across a broad range of mental disorders including psychosis. At present, there are no published treatment studies of non-affected individuals characterised by antecedents (Liu *et al.*, 2010). Following the development of children presenting with antecedents of schizophrenia, as well as children with a family history of schizophrenia, could provide important information on the aetiology of the disorder, and may open opportunities for intervention during the premorbid phase that may be more effective in either delaying or preventing illness onset.

Poor FER may be associated with later schizophrenia through its impact on social functioning (Marwick and Hall, 2008). Among adults with schizophrenia both cognitive function (particularly verbal memory and processing speed) and emotion perception are known to be associated with functional deficits (Couture *et al.*, 2006, Fett *et al.*, 2011, Green, 1996, Irani *et al.*, 2012). Social and role functioning impairments often occur early in the course of the disorder, in the prodromal and premorbid phases of illness, and are present among youth meeting UHR criteria for psychosis (Cornblatt *et al.*, 2012,

Tarbox and Pogue-Geile, 2008). Poor scholastic achievement could reflect difficulties which may be a precursor to later work and role functioning difficulties (Cornblatt *et al.*, 2012). Specific interventions targeting cognitive impairment and perception of emotions may limit future functional disability.

Among individuals with schizophrenia, there is evidence for improvements in cognitive functioning following completion of targeted cognitive interventions (Franck *et al.*, 2013, Wykes *et al.*, 2011). To date, only one study has specifically examined the effects of cognitive training among UHR youth (Rauchensteiner *et al.*, 2011). Ten sessions of cognitive training on tasks of attention, memory, and executive function over a four week period were provided to 10 UHR individuals (mean age 27 years) and 16 individuals with schizophrenia (mean age 30 years). Results indicated that the UHR group made significant gains on most cognitive measures, particularly verbal memory, compared to the schizophrenia group. The improvements in cognitive function in the UHR group suggest an increased neuroplasticity in UHR individuals compared to adults with schizophrenia (Fisher *et al.*, 2012). It is plausible that such gains would be even greater, and potentially more durable, among children presenting ASz and children with a positive family history of schizophrenia or SSD.

Evidence from healthy children shows that targeted cognitive training in specific domains such as memory elicits generalised improvements in other domains of cognitive function such as scholastic achievement (Gathercole *et al.*, 2004, Witt, 2011). Further, a recent study of healthy children, aged on average 10 years, who completed a training programme for 35 minutes a day, for at least 20 days over a five-to-seven week period, to improve working memory skills reported significant improvements in mathematics six months later. The authors suggested that the training may have induced long-term plasticity in brain areas associated with working memory function (Westerberg and Klingberg, 2007).

Interventions that target emotion perception have been successful in improving facial emotion recognition among adults with schizophrenia (Frommann *et al.*, 2003, Russell *et al.*, 2006, Russell *et al.*, 2008, Silver *et al.*, 2004, Wölwer *et al.*, 2005). However, improvements in emotion perception are only meaningful if gains extend beyond laboratory conditions into real-world settings (Roberts and Velligan, 2012). Without improved cognitive function, it is unlikely that targeted emotion perception training would be effective (Roberts and Velligan, 2012).

There are a number of broad-based interventions which, among other aspects, focus on improving both cognitive skills and higher level social skills, for example, Cognitive Enhancement Therapy (CET: Hogarty *et al.*, 2006) and Integrated Psychological Therapy (IPT: Brenner *et al.*, 1994). These interventions involve computer-based cognitive training and social learning. Among adults with schizophrenia, improvements in social cognition and social functioning are evident after completion of these interventions (Hogarty *et al.*, 2006, Roder *et al.*, 2010). The findings from this thesis imply that brief targeted cognitive training might benefit ASz and FHx children, improving cognition and subsequent academic achievement, and also enhancing social and role functioning skills which are known to consolidate during late adolescence (Yung and Mcgorry, 1996a).

10.5 Strengths and Limitations

The strengths and limitations of each study were discussed in their respective chapters. The main points are addressed here.

Within the staging approach to schizophrenia (Keshavan *et al.*, 2011, Mcgorry *et al.*, 2008, Wood *et al.*, 2011), the earliest stage would be risk for the disorder in the absence of observable deficits (Insel, 2010). At present, this earliest stage has yet to be fully characterised. The research reported in this thesis provides new information on the

cognitive and facial emotion processing dysfunctions that are present among children who present other well-replicated antecedents of schizophrenia and among those with affected relatives.

The strengths of each study include: (1) the novel comparison of three groups at-risk for schizophrenia or SSD based on differing definitions of risk (Chapter Six); (2) the assessment a broad array of cognitive functions that have been previously identified as impaired in adults with schizophrenia and with FEP (Mesholam-Gately *et al.*, 2009, Reichenberg and Harvey, 2007) (Chapters Six and Seven); (3) the assessment of cognitive change during childhood and into early adolescence prior to the age-range of risk associated with the development of schizophrenia (Chapter Seven); (4) the inclusion of a typically developing group, thereby, providing information on the trajectory of normal cognitive development as a basis for identifying specific abnormalities that maybe associated with risk for the disorder (Chapter Seven); (5) the use of a statistical procedure for analysing repeated measures over time that was not limited by partially missing data or unequally spaced time assessments (Curran *et al.*, 2010) (Chapter Seven); (6) adjusting for practice effects in statistical models (Chapter Seven); practice effects on cognitive performance have been observed among healthy children/adolescents aged 9-16 years, assessed at three time points at two year intervals (Waber *et al.*, 2012) and may be more prevalent at younger ages (Rabbitt *et al.*, 2008); and, (7) the use of a well-established FER task that permitted comparison of our study findings with those obtained previously with other at-risk or chronic schizophrenia samples (Chapter Nine).

As described in Chapter Three, there were no differences in the prevalence of triad components, including type of PLE reported and impact/distress associated with these experiences, between ASz children recruited into the laboratory assessments relative to those who did not participate further (i.e., ASz and ASz-no children), except

significantly greater odds of not participating if the child reported scores in the abnormal range on the SDQ emotional problems scale. Among TD and TD-no children, the prevalence of "borderline" SDQ psychopathology scores and "somewhat true" PLES did not differ. Consequently, a further strength of this thesis is that ASz and TD children who participated in the studies reported in this thesis are similar in terms of the breakdown in triad components to ASz and TD children identified through school screening procedures who did participate in studies included in this thesis.

The presence of at least one self-reported "somewhat true" response to a PLE questionnaire item characterised over three-quarters of TD and TD-no children, which is consistent with findings indicating that PLEs may form a relatively common feature of children between the ages of 9-12 years (Kelleher *et al.*, 2012a, Laurens *et al.*, 2007, Laurens *et al.*, 2011). In addition, "borderline" SDQ psychopathology scores that were approximately in line with UK SDQ population norms (Goodman, 2001) suggest that TD children included in the thesis were representative of children in the general population. This also suggests that findings from the studies reported in this thesis were not biased by the use of an abnormally "well-control" group that may lead to an over-estimation of effect sizes (Lewis and Pelosi, 1990).

Nonetheless, the findings from the studies presented in this thesis may be subject to alternative sources of bias. For example, ASz children experiencing greater distress and/or impact due to their emotional, social, and behavioural problems may be over represented in the current thesis. Caregivers who experienced concern regarding their child's apparent difficulties may have been more inclined to participate in the research study as a potential source of help or reassurance regarding their child's problems. However, with respect to PLEs, it would appear that ASz children who did not participate in the studies included in the thesis were experiencing greater impact and distress due to these unusual experiences than ASz children who participated. In

addition, as shown in Table 6, the TD participants featured in the thesis were more likely to be white than TD children who did not participate. There is evidence to indicate that individuals who participate in research studies are often of higher SES than individuals who do not participate (Korkeila *et al.*, 2001, Langhammer *et al.*). Such biases could potentially lead to an over-estimation of effect sizes reported in studies included in this thesis.

Only a small number of studies were included in the domains of scholastic achievement and motor function in the meta-analyses reported in Chapter Four. Significant heterogeneity was not reported in the motor function domain, but was observed in the scholastic achievement domain. Due to the small number of studies included in these domains, it was not possible to explore whether heterogeneity was due to differences in education systems or measures of scholastic achievement.

A recent meta-analysis examined changes in cognitive function over –time among individuals with FEP and youth at UHR for psychosis relative to healthy comparison individuals (Bora and Murray, in press). Results indicated improvement in all cognitive domains for all three groups. Importantly, there was no evidence of cognitive decline in UHR individuals associated with the onset of psychosis, indicating that cognitive deficits may already be present when individuals meet UHR criteria (Bora and Murray, in press). This finding is consistent with the results of the meta-analysis reported in Chapter Four which confirmed the presence of lower IQ by 13 years and by 16 years among individuals who develop schizophrenia or SSD in adulthood compared to those who not. However, the meta-analysis reported in Chapter Four focused on cognitive data from one assessment point and thereby could not address the question of changes in cognitive functions as children aged.

Samples sizes of ASz, FHx, and TD groups were relatively small, particularly for the FHx^{H} and FHx^{L} groups in the study of cognitive functions reported in Chapter Six. Nonetheless, already in childhood, those with one first-degree or two second-degree relatives with schizophrenia showed impairment across a range of cognitive domains consistent with several reviews of cognitive functioning in FHx adolescents and young adults (Agnew-Blais and Seidman, 2013, Erlenmeyer-Kimling, 2000, Niemi *et al.*, 2003). Moreover, the results extend previous findings of greater neurocognitive impairment among youth with a first-degree compared to second-degree relative with schizophrenia (Keshavan *et al.*, 2010) to children assessed well before the typical period of risk for the development of schizophrenia.

Sample attrition at follow-up assessments of cognitive functions may have reduced statistical power in our longitudinal analysis. In addition, among adolescents and young people, those who drop out of longitudinal studies are more likely to be of by poorer academic ability, lower socioeconomic status, and poorer physical and psychological health (Granero Pérez *et al.*, 2007, Gustavson *et al.*, 2012). Therefore, the sample who completed cognitive assessments at 24- and 48-months after the baseline assessment may have been biased and thereby the generalisability of the results on change in cognitive function may be limited. Table 4 in Chapter Three indicates that approximately 6% (n=2), 10% (n=3), and 2% (n=1) of ASz, FHx, and TD children declined to participate or were non-contactable at FU24, respectively. At FU48, rates were elevated with 25% (n=8), 17% (n=5), and 7% (n=3) of ASz, FHx, and TD declining to participate or who were non-contactable, respectively. Consistent with existing literature on sample attrition among young people in longitudinal studies, drop-out rates were higher at FU48 than FU24 (Schaffer, 1996), although sample drop-out rates were relatively low compared to rates of 30% to 70% previously identified (Gustavson *et al.*, 2012). Further, drop-out rates were greater among ASz and FHx

groups, who at baseline assessments, were characterised by lower academic achievement and whose parents were characterised by lower occupational status than TD children. However, due to the small number of participants that declined to participate or who were non-contactable at follow-up assessments, it was not viable to statistically investigate this potential bias further.

In Chapter Seven, 12.5% (n=4) of ASz children at FU24 and 6% (n=1) at FU48 were excluded from statistical analyses because they obtained scores on SDQ psychopathology subscales in the "normal range" and they responded "not true" on all nine PLE items. Children were categorised using initial school screening data in order to establish the predictive validity of a novel method of identifying children aged 9-12 years using general population screening by questionnaires for schizophrenia spectrum illness. However, the exclusion of these children from Chapter Seven as well as reducing statistical power, fails to take into account developmental changes in expression and frequency of externalising and internalising behaviours and PLEs (Blandon *et al.*, 2008, Bongers *et al.*, 2004, Kelleher *et al.*, 2012a), which may affect cognitive development.

After adjusting statistical models of longitudinal cognitive function for ethnicity and parent's occupation, differences between the ASz and TD and the FHx and TD youth were attenuated. By contrast, differences in rates of change in performance of both the ASz and FHx youth compared to TD youth remained statistically significant after entering the two covariates into the statistical models. Income-related differences may play in an important role in cognitive development such that children from high income backgrounds perform significantly better than individuals from low income backgrounds on a wide range of cognitive measures (Waber *et al.*, 2007, Waber *et al.*, 2012). The findings from this thesis indicate that the effects of SES and ethnicity differences on cognitive performance may be of greater importance at a younger age.

It is plausible that differences in cognitive function during childhood may reflect a lack of parental involvement in schooling, reading, and early learning activities (Bradley and Corwyn, 2002, Bradley *et al.*, 2001, Evans, 2004, Hart and Risley, 1992). Indeed, evidence indicates that these factors may mediate the relationship between SES and intellectual development (Guo and Mullan-Harris, 2000, Linver *et al.*, 2002). It may be that the importance of parental input and the home environment declines with age as the responsibility for education moves to school (Fryer and Levitt, 2006). Equally, it is possible that inequalities at early stages of cognitive development lead to greater inequalities at later stages of development due to both school (Pallas *et al.*, 1994) and non-school influences (Downey *et al.*, 2004).

Evidence from a prospective longitudinal study of 6,290 Canadian children and adolescents aged 7 to 15 years observed a widening in mathematics achievement between students of lower and higher SES based on a composite measure of SES incorporating family income, parental education, and parental occupational prestige (Caro *et al.*, 2009). Specifically, the authors found that between 7 to 11 years, the gap between low and high SES groups remained stable, but the gap widened at an increasing rate from 11 to 15 years. A widening gap in reading abilities with increasing age between youth from low and high SES backgrounds has also been reported (Cooper *et al.*, 1996) Disparity between the results from the thesis and the above studies may reflect differences in measures used to assess SES. Prospective longitudinal studies that measure cognitive function in children and extend through to late adolescence which examine the effects of SES using different measures are required.

The cross-sectional and prospective longitudinal studies of cognitive function included assessments of IQ made using the WASI (Wechsler, 1999). The study of cognitive performance at the initial assessment that is reported in Chapter Six estimated full-scale IQ from scores of four subtests (vocabulary, block design, similarities, and

matrix reasoning), while in the prospective, longitudinal study of cognitive performance that is reported in Chapter Seven IQ scores were estimated from the scores of two subtests (vocabulary and matrix reasoning). Full-scale IQ scores obtained from the WASI and the Wechsler Intelligence Scale for Children – 4th edition (WISC-IV: Wechsler, 2003) show strong correlations. However, the baseline assessment measured a mean IQ score of approximately one SD above manual-derived norms for TD children, though performance on the scholastic achievement domain for these TD children was in line with UK population norms. In addition, a study examining the reliability of the WASI compared to the Wechsler Adult Intelligence Scale-III (WAIS-III: Wechsler, 1997) among 72 adult males from a veterans centre in USA, found that the WASI was significantly less accurate than the WAIS on predicting verbal IQ (verbal comprehension), performance IQ (perceptual reasoning), and full scale IQ (Axelrod, 2002). A significant decline in IQ was observed among TD and ASz children between 9 and 15 years, may indicate that the IQ scores at the initial assessment were inflated. The outdated and small normative sample sizes (n=~30 in each age band up to 16 years) used within the WASI (Wechsler, 1999) may have comprised the ability of this thesis to characterise group differences in IQ.

A further limitation of the thesis was that measures of alcohol and drug use, and most particularly of cannabis use, were not included. Adolescents who use cannabis generally begin using around 12 to 16 years (Shrivasta *et al.*, 2011) and among some, early and heavy cannabis use has been shown to increase the risk for psychotic disorders (Di Forti *et al.*, 2009, Moore *et al.*, 2007). Evidence also indicates that increased dopamine synthesis capacity characterises patients with psychosis and individuals meeting UHR criteria who later transition to psychosis (Egerton *et al.*, 2013, Howes and Kapur, 2009, Howes *et al.*, 2007) However, recent evidence indicated that reduced dopamine synthesis capacity was associated with an earlier age of cannabis use among

young adults experiencing PLEs (Bloomfield *et al.*, in press). Authors suggest that cannabis use during critical periods of development, such as adolescence, may alter dopaminergic function and underlie risk for psychosis (Bloomfield *et al.*, in press). The results of changes in IQ with age may reflect early cannabis use among ASz, FHx, and TD youth. Cross-sectional studies indicate that poor cognitive function is associated with a younger age of onset of cannabis use (Fontes *et al.*, 2011, Gruber *et al.*, 2012, Pope *et al.*, 2001). Recent evidence from a prospective birth cohort study reported a decline in IQ from childhood into adulthood among adolescent-onset cannabis users (Meier *et al.*, 2012). However, cannabis use is also associated with better premorbid cognitive functioning among adults with schizophrenia and individuals experiencing FEP (Cunha *et al.*, 2013, Yücel *et al.*, 2012). Thus, further research on the interaction between cannabis use and adolescent cognitive development and risk for schizophrenia or SSD is required.

The findings described in Chapter Nine of this thesis indicate that FER performance and the misperceptions of emotions by ASz children were not associated with the emotional problem subscale of the SDQ (Goodman, 2001) reported on screening questionnaires. However, there is consistent evidence to indicate that depressed individuals have difficulties in accurately perceiving neutral facial emotion expressions; specifically, a negative response bias towards identifying neutral expressions as sad (Bourke *et al.*, 2010, Gur *et al.*, 1992, Leppanen *et al.*, 2004). A negative bias towards sadness may contribute to the impaired interpersonal functioning observed among individuals with depression (Hale *et al.*, 1998), and to the social withdrawal reported recently among ASz children as compared to TD children (Matheson *et al.*, 2013). In addition, a recent review of FER among individuals with social anxiety disorder found evidence of a negative response bias in the interpretation of facial emotion expressions (Machado-De-Sousa *et al.*, 2010). Unfortunately, the study sample under-represented

the prevalence of emotional symptoms typical of the population of ASz children reported in Table 7. Low statistical power thus prevented the examination of the relationship between depression/anxiety symptoms and FER performance among ASz children. Consequently, it is not known whether the findings of Chapter Nine reflect in part, ASz children's mood at time of FER assessment.

Psychological models of face processing comprise multiple functional components including visual processing, face recognition and facial emotion identification (Bruce and Green, 1986, Calder and Young, 2005, Ellis and Young, 1988). There is some evidence that the basic visual processing of faces (i.e., the detection of physical features of the face rather than the face recognition/perception, or facial emotion identification processes), may be impaired in schizophrenia (Chen *et al.*, 2008). In addition, deficits in facial perception have been identified in some, though not all, studies of adults with schizophrenia (Marwick and Hall, 2008), particularly in tasks which place additional memory and attentional demands on participants (Hooker and Park, 2002, Whittaker *et al.*, 2001). In order to investigate the specificity of facial emotion processing deficits in schizophrenia, a number of studies have included a task requiring the processing of non-facial information. Although tasks of face perception are often included in studies of facial emotion recognition among adults with schizophrenia, to date only one study of individuals at-risk for schizophrenia has included a face recognition control task (Van Rijin *et al.*, 2011). Using the Benton and Van Allen test, Van Rijin and colleagues reported a mean percentage of correct responses of 90% and 89% for the control and UHR group, respectively. The authors concluded that adolescents at UHR for psychosis are characterised by impairments in labelling facial expressions, but retain the capacity to recognise faces. Thus, a further limitation of Chapter Nine of this thesis is that FER difficulties observed among ASz children might also be due deficits in the basic identification/perception of faces that were not examined.

Recent meta-analyses of patient-control, prospective- and cross-sectional cohort studies, and retrospective studies, indicate an association between childhood trauma and risk for psychosis (Bonoldi *et al.*, in press, Matheson *et al.*, 2011, Varese *et al.*, 2012). An association between childhood experiences of trauma and risk for PLEs has also been observed (Heins *et al.*, 2011, Kelleher *et al.*, 2013). Further, adults with psychosis reporting a history of auditory hallucinations were reported to have experienced significantly more sexual, emotional, and physical abuse than patients without a history of auditory hallucinations (Sheffield *et al.*, 2013). It is known that ASz children experienced a greater number of daily life stressors and that they were more sensitive to these stressors, whilst FHx children reported a greater number of negative life events and were distressed by these experiences (Cullen *et al.*, submitted). However, the extent of childhood maltreatment or trauma (e.g., sexual abuse, physical abuse, and emotional abuse) among children in CHADS is currently unknown.

Trauma during childhood has been linked to poor cognitive and facial emotion processing functioning in childhood and adulthood (Aas *et al.*, 2011, Mezzacappa *et al.*, 2001, Perez and Widom, 1994, Pollack and Sinha, 2002, Pollak and Kistler, 2002). Converging evidence suggests that maltreated youth exhibit dysfunctional patterns of facial emotion perception perhaps borne out of the way in which children with a history of trauma adapt to unpredictable and frightening environments (Pollack, 2003). Specifically, maltreated children appear to display distinctive processing of emotion towards angry facial expressions (Pollack and Sinha, 2002, Pollak and Kistler, 2002). Therefore, it is not known whether childhood trauma may be associated with the deficits in facial emotion recognition shown by the ASz children.

10.6 Final conclusions

Existing early identification approaches are based on a positive family history, UHR criteria, or the presence of PLEs during childhood and adolescence. However, a

positive family history of schizophrenia or SSD identifies only a subset of children who develop the illness and may be an imprecise measure of genetic risk, UHR criteria identifies vulnerable individuals at imminent risk of psychosis, and PLEs constitute a non-specific marker of risk for later psychiatric disorders. Thus, there was a need to establish other at-risk strategies in order to maximise opportunities for early intervention. The goal of this thesis was to assess the utility of a novel strategy to identify children aged 9-12 years presenting a triad of known antecedents of schizophrenia (motor and/or speech delays, clinically relevant internalising and/or externalising problems, and psychotic like-experiences). Only follow-up of ASz children will establish the degree to which the antecedent triad predicts later psychotic or non-psychotic disorders. The results of the present thesis suggest that the measurement and definition of ASz identifies children who present deficits in cognitive and facial emotion processing domains similar to those presented by children who later in life developed schizophrenia or to adults with schizophrenia.

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Appendix I

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ORIGINAL ARTICLE

Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia

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Background. Previous reviews have reported cognitive and motor deficits in childhood and adolescence among individuals who later develop schizophrenia. However, these reviews focused exclusively on studies of individuals with affected relatives or on population/birth cohorts, incorporated studies with estimated measures of pre-morbid intelligence, or included investigations that examined symptomatic at-risk participants or participants 18 years or older. Thus, it remains unclear whether cognitive and motor deficits constitute robust antecedents of schizophrenia. Meta-analyses were conducted on published studies that examined cognitive or motor function in youth aged 16 years or younger who later developed schizophrenia or a schizophrenia spectrum disorder (SSD) and those who did not.

Method. Twenty-three studies fulfilled the following inclusion criteria: (1) written in English; (2) prospective investigations of birth or genetic high-risk cohorts, or follow-back investigations of population samples; (3) objective measures of cognitive or motor performance at age 16 or younger; (4) results provided for individuals who did and who did not develop schizophrenia/SSD later in life; and (5) sufficient data to calculate effect sizes. Four domains of function were examined: IQ; Motor Function; General Academic Achievement; and Mathematics Achievement.

Results. Meta-analyses showed that, by age 16, individuals who subsequently developed schizophrenia/SSD displayed significant deficits in IQ ($d = 0.51$) and motor function ($d = 0.56$), but not in general academic achievement ($d = 0.25$) or mathematics achievement ($d = 0.21$). Subsidiary analysis indicated that the IQ deficit was present by age 13.

Conclusions. These results demonstrate that deficits in IQ and motor performance precede the prodrome and the onset of illness.

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Key words: Child, high-risk, intelligence, psychosis, school performance.

Introduction

Evidence has accumulated to indicate that schizophrenia is, in part, a neurodevelopmental disorder (Murray & Lewis, 1987; Weinberger, 1987) characterized by abnormal functioning during childhood and adolescence (Niemi *et al.* 2003; Schenkel & Silverstein, 2004). Converging evidence from prospective longitudinal studies of population cohorts, prospective studies of individuals at elevated risk of schizophrenia because they have a family history of the illness, and 'follow-back' studies of adults with schizophrenia suggest that cognitive and motor dysfunctions precede the onset of schizophrenia. However, past literature reviews of cognitive functioning among children who develop schizophrenia/schizophrenia spectrum disorders (SSD) in adulthood have been limited in several respects: (i) they have focused exclusively on individuals with affected relatives (Niemi *et al.* 2003; Keshavan *et al.* 2010) or on population and/or birth cohorts (MacCabe, 2008; Welham *et al.* 2009*a*); (ii) they have not followed samples into adulthood and assessed them for schizophrenia/SSD; or (iii) they have included studies with estimated measures of premorbid intellectual functioning assessed in adulthood

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when the participant already had a diagnosis of schizophrenia (Schenkel & Silverstein, 2004). Thus, it remains unclear whether cognitive and motor deficits constitute robust antecedents of schizophrenia.

During childhood, individuals who subsequently developed schizophrenia or SSD, compared to those who did not, were characterized by lower IQ (Woodberry *et al.* 2008) and poorer motor function (Walker *et al.* 1994; Rosso *et al.* 2000; Cannon *et al.* 2002, 2006; Schiffman *et al.* 2004). Additional cognitive decline prior to the onset of the prodromal phase of schizophrenia has been reported (Fuller *et al.* 2002; Osler *et al.* 2007). Academic achievement has also distinguished children who later developed schizophrenia/SSD, although findings have differed according to subject and assessment type (Watt & Lubensky, 1976; Jones *et al.* 1994; Crow *et al.* 1995; Fuller *et al.* 2002; Bilder *et al.* 2006; MacCabe *et al.* 2007). Furthermore, five studies reported no differences in pre-morbid academic performance (Isohanni *et al.* 1998; Cannon *et al.* 1999; Isohanni *et al.* 1999; Helling *et al.* 2003; Ang & Tan, 2004), which may reflect differences in the education systems characterizing the study cohorts. Taken together, the extant literature suggests that individuals who develop schizophrenia present poorer cognitive abilities in childhood than those who never develop schizophrenia/SSD. To date, little is known about the age at which these deficits emerge or their specific nature.

Two previous, widely cited, meta-analyses evaluated IQ among individuals who subsequently developed schizophrenia, and both yielded medium-sized deficits (Aylward *et al.* 1984; Woodberry *et al.* 2008). The present meta-analysis differs from the more recent of these, by Woodberry and colleagues, in several ways. First, several studies that were included in that meta-analysis reported the results of IQ assessments completed at multiple ages spanning a broad age range of 3–19 years (Albee *et al.* 1964; Watt & Lubensky, 1976; Jones *et al.* 1994; Ott *et al.* 1998; Cannon *et al.* 2000, 2002; Seidman *et al.* 2006). An overall unweighted mean effect size was calculated for each of these studies spanning multiple assessments and a broad age range, thereby providing a less robust estimate of pre-morbid IQ than might be achieved by using a single assessment completed during childhood/adolescence. Second, the previous meta-analysis included studies of symptomatic, help-seeking individuals meeting inclusion criteria for treatment in an intervention programme for persons at ultra-high risk for psychosis (Brewer *et al.* 2005; Lencz *et al.* 2006), and studies examining IQ among young adults (Lubin *et al.* 1962; Zammit *et al.* 2004; Reichenberg *et al.* 2005; Kremen *et al.* 2006; Whyte *et al.* 2006). Given that intellectual deficits have been reported to increase in magnitude with the onset of psychosis (Rabinowitz *et al.* 2000; Gunnell *et al.* 2002; Caspi *et al.* 2003), the effect sizes of the difference between participants who did and who did not develop schizophrenia in these studies may reflect some early prodromal disease process rather than an antecedent of schizophrenia. Third, although the previous meta-analysis included subanalyses that examined IQ by narrower age bands, only three studies were included in the meta-analysis that assessed participants aged 13 years or younger. Finally, unlike both previous meta-analyses that focused solely on IQ (Aylward *et al.* 1984; Woodberry *et al.* 2008), the present meta-analysis includes examination of additional domains of academic achievement and motor functioning.

The aim of the present meta-analyses was to examine IQ, motor function and academic achievement in children and young adolescents (aged $\leqslant$16 years) who subsequently developed schizophrenia/SSD. A recent review of studies on individuals at ultra-high risk for psychosis indicated a typical age of onset of basic prodromal symptoms of greater than 16 years (Ruhrmann *et al.* 2010). By restricting the meta-analyses to studies of children aged 16 years or younger, the present meta-analyses aimed to determine whether deficits in IQ, motor function and academic achievement are present before the typical age of onset of the prodrome.

Method

Sample

Meta-analyses were conducted to identify the effect sizes of differences in scores obtained on cognitive and motor performance measures by individuals aged 16 years or younger who subsequently developed schizophrenia compared to those who did not. Articles were identified through literature searches conducted in PubMed/Medline and PsycINFO, using the keywords 'schizophrenia' and 'IQ' or 'intelligence' or 'motor' or 'school' or 'scholastic' and 'premorbid' or 'prospective' or 'cohort' or 'high risk'. References from articles and relevant literature reviews were also examined for possible inclusion in meta-analyses. Inclusion criteria were: (1) written in English; (2) published or unpublished prospective investigations of birth cohorts or genetic high-risk samples, or follow-back investigations of population samples; (3) objective measures of cognitive or motor function when participants were aged 16 or younger; (4) results provided for cohort members who did and who did not develop schizophrenia or an SSD later in life; and (5) sufficient data to calculate effect sizes.

The initial literature search by the first author identified 2623 studies, of which 34 fulfilled the inclusion criteria. A co-author independently reviewed these studies to verify that inclusion criteria were met. Among the 34 studies, 10 contained samples that overlapped (Lane & Albee, 1963, 1968; Albee *et al.* 1964; Cannon *et al.* 2000, 2002, 2006; Niendam *et al.* 2003; Seidman *et al.* 2006). To avoid multiple entries on the same sample, only data from the study containing the largest number of participants were analysed (Albee *et al.* 1964; Cannon *et al.* 2000, 2002; Seidman *et al.* 2006). Ten studies reported assessments of participants at multiple ages ranging from 3 to 19 years (Watt & Lubensky, 1976; Jones *et al.* 1994; Crow *et al.* 1995; Ott *et al.* 1998; Cannon *et al.* 2000, 2002; Rosso *et al.* 2000; Ang & Tan, 2004; Bilder *et al.* 2006; Welham *et al.* 2009*b*). From these studies, only the results from a single assessment completed when participants were between 4 and 14 years old were included in the meta-analyses. Seven studies reported insufficient data to calculate an effect size (Ambelas, 1992; Crow *et al.* 1995; Cannon *et al.* 1999, 2006; Erlenmeyer-Kimling *et al.* 2000; Fuller *et al.* 2002; Walker *et al.* 2002). Additional data from authors were obtained for all but two studies (Ambelas, 1992; Walker *et al.* 2002), but data from two studies remained insufficiently detailed to satisfy the inclusion criteria (Erlenmeyer-Kimling *et al.* 2000; Fuller *et al.* 2002). Two other papers reported similar data (Isohanni *et al.* 1998, 1999); only data in the 1998 publication were included in the meta-analyses. Two studies that reported IQ scores for participants aged between 8 and 20 years were excluded (Bower *et al.* 1960; Sørensen *et al.* 2006). Another study, which presented results for performance IQ between members of a rubella-exposed birth cohort who subsequently developed schizophrenia and those who did not, was also excluded from the meta-analysis (Brown *et al.* 2001).

Meta-analyses were performed using the results from the 23 studies that fulfilled the inclusion criteria. The results were categorized into four domains of cognitive and motor function. Table 1 presents details of each study included in the meta-analyses, with a description of the sample, participant age at assessment, the test instrument used, and effect sizes denoting the difference in performance between the participants who subsequently developed schizophrenia/SSD compared to those who did not. Across all 23 studies, the age of the participants at the time of assessment ranged from 2 to 16 years. Twenty-one of the 23 studies included males and females whereas two examined only males (Ang & Tan, 2004; Osler *et al.* 2007). The comparison groups varied widely across studies, and were described as classmates, child psychiatric patients with no adult mental disorder, members of birth cohorts who did not develop schizophrenia/SSD, members of birth cohorts who did not develop any major mental disorder, and participants with or without a family history of schizophrenia/SSD.

Statistical analyses

Meta-analyses were conducted with Stata version 10 (Stata Corporation, USA) using a random effects model (Dersimonian & Laird, 1986) that assumes that the effects being investigated in a set of studies are a random sample drawn from a population of possible effect sizes. Meta-analyses were performed on difference scores for each domain of functioning, comparing participants who developed schizophrenia/SSD to those who did not. Difference scores were standardized by calculating Cohen's *d* effect sizes (Cohen, 1988) and interpreted according to effect size indices of 'small (0.2)', 'medium (0.5)' and 'large (0.8)' (Cohen, 1992). The summary effect sizes for each domain were the standardized mean differences (SMDs), weighted by the precision of the SMD. For each SMD, a *z* value and a significance level provided an indication of the two-sided statistical significance of the association at the 95% probability level. For the IQ domain, the effect size from one study was an extreme outlier (Woodberry *et al.* 2008), so the analysis was conducted with and without the inclusion of this study (Amminger *et al.* 2000).

The significance and the magnitude of heterogeneity across studies were calculated using the *Q* statistic and I^2 statistic. Where there was significant heterogeneity within a domain, and where there were sufficient studies to provide adequate statistical power (i.e. for IQ only), effect size moderators were examined. Three potential moderator variables were examined: comparison group, IQ assessment instrument, and disorder outcome. Comparison group (matched comparison group or unselected cohort) was included as it had been reported to be a significant source of heterogeneity in a previous meta-analysis on IQ (Woodberry *et al.* 2008). An instrument used to assess IQ (i.e. Wechsler Intelligence Scales or other test) was included as different types of IQ tests, particularly tests that are older, may provide variable estimates of IQ (Sattler, 2001). We also examined disease outcome (i.e. schizophrenia or SSD) based on the rationale that individuals who develop schizophrenia may differ from those who develop SSD. For each variable, a regression model was estimated using an unrestricted maximum likelihood model. Publication bias was assessed graphically and statistically using published methods (Begg & Mazumdar, 1994; Egger *et al.* 1997).

Table 1. *Study details and effect sizes for meta-analyses*

Study	Sample	Schizophrenia/SSD		Age at assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
IQ						
Albee *et al.* (1964)	A follow-back study of adults from Cleveland, USA	154 Schizophrenia patients recruited from hospital in-patient unit	4166 Children in same school year	11–12	Cleveland classification IQ test	0.64[b]
Offord (1974)	A follow-back study of white adults from Pennsylvania, USA	116 Schizophrenia patients (including those with a diagnosis of mild to moderate retardation) recruited from in-patient unit: 51 males, 65 females	116 School classmates matched on ethnicity, sex and social class of origin: 51 males, 65 females	During first 9 years of school (exact age not given)	Group administered IQ test	0.69[b]
Watt & Lubensky (1976)	A follow-back study of adults from Massachusetts, USA	36 Schizophrenia patients recruited from hospital in-patient unit	36 School classmates matched on sex, ethnicity and social class of origin	4–12	Kuhlman–Anderson IQ test/Otis self-administration test	0.49[b]
Jones *et al.* (1994)	British birth cohort born 1946	30 Cohort members with a diagnosis of schizophrenia: 20 males, 10 females	4715 Cohort members without schizophrenia: 2457 males, 2259 females	11	Group administered IQ test	0.30[b]
Crow *et al.* (1995)	British birth cohort born 1958	29 Cohort members with a diagnosis of schizophrenia	1446 Cohort members with no psychiatric hospital admission	11	General ability IQ test	0.62[b]
Ott *et al.* (1998)	New York High-Risk Project	18 Study participants with a diagnosis of schizophrenia or SDD	189 Study participants from a similar school district with no mental disorder in adulthood	7–12	WISC-R IQ	0.78[b]
Cannon *et al.* (2000)	Birth cohort born 1959–1966 from Philadelphia, USA	57 Cohort members with a diagnosis of schizophrenia or SSD: 41 males, 16 females	5829 Cohort members with no mental disorder in adulthood: 2865 males, 2964 females	7	WISC	0.53[b]
Amminger *et al.* (2000)	A follow-back study of adults born 1960–1971 in Vienna	8 Child psychiatric patients with a diagnosis of schizophrenia or SSD in adulthood	13 Child psychiatric patients with no diagnosis in adulthood	⩽16	WISC	1.85[b]
Cannon *et al.* (2002)	Birth cohort born 1972–1973 from Dunedin, New Zealand	32 Cohort members with a diagnosis of SSD	579 Cohort members with no diagnosis of SSD, mania or anxiety/depression	11	WISC	0.44[b]

Seidman *et al.* (2006)	Birth cohort born 1959–1965 from New England, USA	31 Cohort members with a diagnosis of schizophrenia: 79.4% males, 20.6% females	61 Cohort members with no diagnosis of SSD, bipolar disorder, recurrent depressive disorder, suicide attempts or psychiatric hospitalizations in adulthood: 54.8% males, 45.2% females	7	WISC	0.65[b]
Osler *et al.* (2007)	Danish birth cohort of males born in 1953	87 Cohort members with a diagnosis of schizophrenia	6790 Cohort members who also completed a cognitive assessment at 18 years	12	Harnquist IQ test	0.14[b]
Welham *et al.* (2009*b*)[c]	Birth cohort born 1981–1984 from Brisbane, Australia	53 Cohort members with a diagnosis of non-affective psychosis.	3204 Cohort members without a diagnosis of non-affective psychosis in adulthood	14	Raven's Standard Progressive Matrices Test	0.35[b]
Sørensen *et al.* (2010)	Study participants drawn from Copenhagen Perinatal Cohort, individuals born 1959–1961	32 Study participants with a diagnosis of SSD	133 Study participants with no psychiatric diagnosis in adulthood	10–13	WISC	0.45[b]
Motor Function						
Walker *et al.* (1994)	A follow-back study of adults from Atlanta, USA	30 Schizophrenia patients recruited from hospital in-patient unit: 23 males, 7 females	21 Adults with no family history of mental disorders: 7 males, 14 females	2–15	Motor skills ratings (from childhood home videos)	0.39[b]
Rosso *et al.* (2000)	Birth cohort born 1959–1966 from Philadelphia, USA	66 Cohort members with a diagnosis of schizophrenia or SSD	6473 Cohort members with no mental disorder in adulthood	7	Motor coordination test	0.48[b]
Cannon *et al.* (2002)	Birth cohort born 1972–1973 from Dunedin, New Zealand	24 Cohort members with a diagnosis of SSD	579 Cohort members with no diagnosis of SSD, mania or anxiety/depression	9	Basic Ability Motor Test	0.73[b]
Schiffman *et al.* (2004)	Study participants drawn from Copenhagen Perinatal Cohort, comprising individuals born 1959–1961	32 Study participants with a diagnosis of schizophrenia	133 Study participants with no mental disorder in adulthood	11–13	Motor coordination scale.	0.69[b]
Academic Achievement: General						
Isohanni *et al.* (1998)	Northern Finland birth cohort 1966	84 Cohort members with a diagnosis of schizophrenia: 54 males, 30 females	10414 Cohort members with no psychiatric hospital admission: 5245 males, 5169 females	16	School marks for all theoretical subjects	0.19[b]
Cannon *et al.* (1999)	Helsinki birth cohort born 1951–1960	400 Cohort members with a diagnosis of schizophrenia or SSD	408 Cohort members with a diagnoses other than schizophrenia	11	Year 4 examination results	0.02[b]
Ang & Tan (2004)	A follow-back study of military servicemen from Singapore	30 Military servicemen with a diagnosis of first-episode psychosis	30 Military servicemen without a past or current mental disorder	12	Primary school leaving examination (average score)	0.05

Table 1 (*cont.*)

Study	Sample	Schizophrenia/SSD		Age at assessment (years)	Domain measure	Effect size[a]
		Present	Absent			
Bilder *et al.* (2006)	A follow-back study of adults from New York	59 Study participants with a diagnosis of schizophrenia or SDD recruited from an in-patient unit	26 Study participants recruited from newspaper advertisements. No mental disorder and matched for sex and age	10–11	Fifth grade achievement test results	0.53[b]
MacCabe *et al.* (2007)	Population-based historical cohort study of adults born 1973–1983 in Sweden	493 Cohort members with a diagnosis of schizophrenia: 318 males, 175 females	713876 Cohort members with no diagnosis: 364967 males, 348909 females	15–16	Swedish National Examination grade point average	0.52[b]
Academic Achievement: Mathematics						
Jones *et al.* (1994)	British birth cohort born 1946	30 Cohort members with a diagnosis of schizophrenia: 20 males, 10 females	4716 Cohort members without schizophrenia: 2457 males, 2259 females	11	Group administered Maths test	0.41[b]
Crow *et al.* (1995)	British birth cohort born 1958	29 Cohort members with a diagnosis of schizophrenia	1446 Cohort members with no psychiatric hospital admission	11	Group Maths administered test	0.48[b]
Helling *et al.* (2003)	A follow-back study of adults born in Sweden	59 Study participants with a diagnosis of schizophrenia or SSD recruited from an in-patient unit	119 School classmates before/after each case	12	End of year teacher assigned grades	0.14[b]
Ang & Tan (2004)	A follow-back study of military servicemen from Singapore	30 Military servicemen with a diagnosis of first-episode psychosis	30 Military servicemen without a past or current mental disorder	12	Primary school leaving examination	0.33

SSD, Schizophrenia spectrum disorder; WISC-R, Wechsler Intelligence Scale for Children – Revised.

[a] Effect sizes were estimated using Cohen's *d*, obtained using sample sizes, means and standard deviations for a group who later developed schizophrenia or an SSD and a comparison group, except for the following: (i) IQ: for Offord (1974), the results were presented across gender, so data were collapsed and overall means and standard deviations were used; for Watt & Lubensky (1976), the effect size was computed from the sample size and *t* statistic; for Jones *et al.* (1994), effect sizes were taken from the Woodberry *et al.* (2008) meta-analysis; for Crow *et al.* (1995), effect size was estimated from the sample size and *f* statistic; for Welham *et al.* (2009*b*), effect size was calculated by converting β to *t* statistics (b/seb) with effect size derived from *t* statistic and sample size for both males and females. A mean weighted effect size was then calculated based on sample size by gender. (ii) Motor Function: for Rosso *et al.* (2000), the odds ratio was transformed into a Cohen's *d* using a method outlined by (Chinn, 2000). (iii) Academic Performance: Mathematics: for both Jones *et al.* (1994) and Helling *et al.* (2003), sample size and *f* statistics were used; and for Crow *et al.* (1995), *t* statistic was calculated from degrees of freedom and *p* value given in paper; effect size was then estimated from sample size and *t* statistic.

[b] Positive values indicate better performance in the comparison group.

[c] Sample size for males and females were taken from measures of attentional dysfunction because not available for Raven's Standard Progressive Matrices Test.

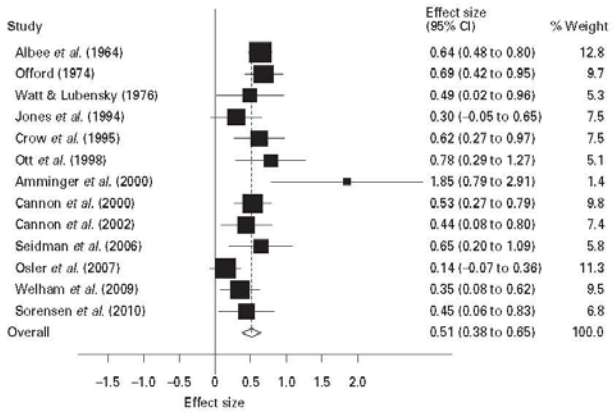

Fig. 1. Forest plot for IQ.

In domains with five studies or less, publication bias could not be explored (Sutton *et al.* 2000).

Results

IQ

A meta-analysis of the 13 studies included in the IQ domain indicated that youth aged 16 years or younger who subsequently developed schizophrenia/SSD obtained lower IQ scores than youth who did not develop these disorders. As illustrated in Fig. 1, a medium effect size was obtained [SMD 0.51, 95% confidence interval (CI) 0.38–0.65, $z=7.51$, $p<0.001$]. Significant heterogeneity was detected across studies ($Q=26.55$, df = 12, $p<0.05/I^2=54.8\%$), but neither comparison group, IQ measure nor diagnostic outcome explained the heterogeneity. No publication bias was detected. After removing one study from the meta-analysis due to an effect size that was an outlier to the group (Amminger *et al.* 2000), the observed effect size remained of medium magnitude (SMD 0.49, 95% CI 0.37–0.61, $z=8.03$, $p<0.001$). Significant heterogeneity was detected ($Q=20.25$, df = 11, $p<0.05/I^2=45.7\%$). Again, neither comparison group, IQ measure nor diagnostic outcome was associated with heterogeneity.

The meta-analysis was repeated after excluding two studies that assessed participants between the ages of 14 and 16 years (Amminger *et al.* 2000; Welham *et al.* 2009*b*). All participants in the remaining 11 studies were aged 13 years or younger. This analysis yielded an effect size that was similar in magnitude to that calculated for participants aged 16 years or younger (SMD 0.51, 95% CI 0.38–0.64, $z=7.69$, $p<0.001$). As before, significant heterogeneity was detected ($Q=19.11$, df = 10, $p<0.05/I^2=47.7\%$). Again, heterogeneity was not associated with the type of comparison group, the measure of IQ or the outcome diagnosis of schizophrenia or SSD. No publication bias was detected.

Motor function

Of the four studies included in the motor function domain, the results from the meta-analysis showed that individuals aged 16 years or younger who subsequently developed schizophrenia/SSD, as compared to those who did not, displayed significant deficits in motor function (see Fig. 2) that were moderate in size (SMD 0.56, 95% CI 0.38–0.74, $z=6.25$ $p<0.001$). No significant heterogeneity was detected across studies ($Q=1.87$, df = 3, $p=0.60/I^2=0.0\%$).

Academic Achievement

General

Five studies examined General Academic Achievement among youth aged 16 years or younger who subsequently developed schizophrenia/SSD, and the results indicated poorer overall academic achievement compared to youth who did not later develop schizophrenia/SSD (see Fig. 3). However, the effect size of the group difference was small and non-significant (SMD 0.25, 95% CI −0.03 to 0.53, $z=1.74$, $p=0.08$). Significant heterogeneity in the results was detected ($Q=40.72$, df = 4, $p<0.001/I^2=90.2\%$), but could not be examined further given the limited number of studies comprising this domain.

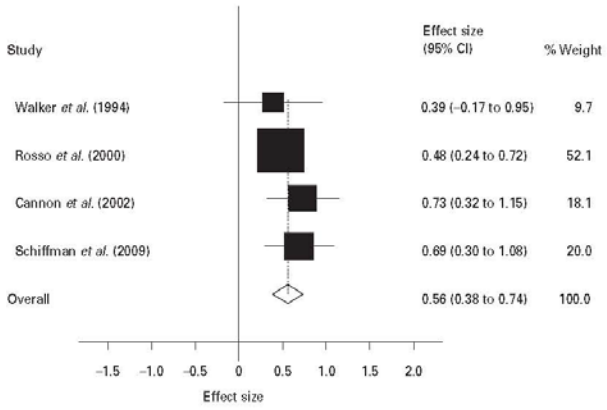

Fig. 2. Forest plot for motor function.

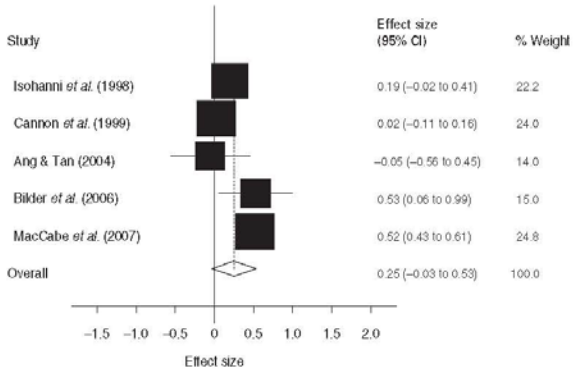

Fig. 3. Forest plot for Academic Achievement: General.

Mathematics

The results of the meta-analysis of four studies showed that youth aged 16 years and younger who later developed schizophrenia/SSD, as compared to those who did not, achieved more poorly on tests of mathematics. However, as indicated in Fig. 4, the effect size of the difference between the two groups was small and non-significant (SMD 0.21, 95% CI −0.09 to 0.51, $z=1.40$, $p=0.16$). Significant heterogeneity was detected ($Q=7.96$, $df=3$, $p<0.05/I^2=62.3\%$), but could not be examined further because of an insufficient number of studies within the domain.

Discussion

To our knowledge, these are the first meta-analyses examining both cognitive and motor performance among youth aged 16 years or younger who later developed schizophrenia/SSD. The meta-analyses demonstrate that participants who subsequently developed schizophrenia/SSD displayed lower IQ and poorer motor function by age 16 than individuals who did not develop these disorders. Furthermore, there were sufficient studies to conduct a meta-analysis that showed that the deficit in IQ was present by age 13. By contrast, overall academic achievement and performance on tests of mathematics did not significantly distinguish those who subsequently developed schizophrenia/SSD from those who did not. These results extend previous findings by establishing that low IQ and impaired motor performance precede the prodrome and onset of illness.

Although significant heterogeneity was detected in the meta-analyses of IQ and the two domains of academic performance, the factors affecting heterogeneity

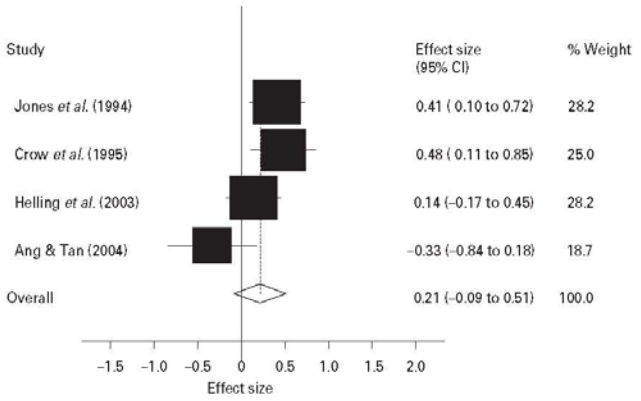

Fig. 4. Forest plot for Academic Achievement: Mathematics.

could be examined only for IQ. Analyses indicated that heterogeneity reported for the IQ results was not due to the type of comparison group used (matched comparison or unselected cohort), the test used to assess IQ (Wechsler or other) or diagnostic outcome (schizophrenia or SSD).

The present meta-analyses obtained the same medium effect size for the difference in IQ by age 16 and by age 13 ($d = 0.51$), between individuals who did and who did not develop schizophrenia/SSD later in life. The present IQ meta-analysis included results from five studies (Crow *et al.* 1995; Amminger *et al.* 2000; Osler *et al.* 2007; Welham *et al.* 2009*b*; Sørensen *et al.* 2010) that had not been included in previous meta-analyses (Aylward *et al.* 1984; Woodberry *et al.* 2008). Nevertheless, the effect sizes obtained in the present analyses by age 16 and by age 13 are similar in magnitude to that reported in a previous meta-analysis ($d = 0.54$) that included participants who were symptomatic or deemed to be at risk for psychosis (Woodberry *et al.* 2008). Thus, our meta-analyses indicate that, among individuals who later develop schizophrenia/SSD, a deficit in IQ is measurable by early to mid-adolescence.

Consistent with the findings of a previous meta-analysis (Woodberry *et al.* 2008), our current analysis indicated that the specific measure of IQ used did not account for significant heterogeneity in the results. Unlike the present meta-analysis, however, Woodberry *et al.* (2008) reported that the type of comparison group (i.e. unselected cohort *versus* matched comparison group) accounted for significant effect-size heterogeneity. Their finding was attributed primarily to the inclusion of one study of 18-year-old military conscripts that used an army classification battery to assess IQ (Lubin *et al.* 1962).

It was not possible to examine all potential moderator variables in the meta-analysis of IQ. This was because of the relatively small number of studies that met inclusion criteria and the limited data available from each study. Examining a larger number of potential moderators may increase the likelihood of drawing false positive conclusions (Thompson & Higgins, 2002). Given the evidence that the prevalence of schizophrenia is higher in males than in females (Aleman *et al.* 2003; McGrath *et al.* 2004), it is possible that gender differences may have contributed to the heterogeneity of the results in the IQ domain, as reported in one previous meta-analysis (Aylward *et al.* 1984), but not in another (Woodberry *et al.* 2008). Unfortunately, the data available for inclusion in the present study were insufficient to permit statistical analysis of gender differences. Five studies included in the present meta-analysis reported the prevalence of schizophrenia separately by gender, and all but one (Welham *et al.* 2009*b*) found higher rates among males than females (Offord, 1974; Jones *et al.* 1994; Cannon *et al.* 2000; Seidman *et al.* 2006). In these studies, the effect sizes of the differences in IQ of participants who did and who did not develop schizophrenia/SSD ranged from small to medium. Only two studies included in the present meta-analysis reported IQ scores separately for males and females (Offord, 1974; Welham *et al.* 2009*b*). These studies indicated that, among the participants who subsequently developed schizophrenia, the males obtained lower IQ scores than the females. However, we did not observe a larger effect size in a study that examined only males (Osler *et al.* 2007) than in studies that included both males and females.

It is unclear whether lower than average IQ is an antecedent specific to schizophrenia. Lower than

average IQ has been reported to characterize children (Van Os *et al.* 1997; Koenen *et al.* 2009) and young adults, particularly males (Zammit *et al.* 2004; Mortensen *et al.* 2005; Tiihonen *et al.* 2005; Urfer-Parnas *et al.* 2009), who subsequently develop mental disorders other than schizophrenia. However, these findings are inconsistent and several studies have failed to identify IQ differences among children/adolescents who subsequently developed bipolar disorder (Cannon *et al.* 2002; Reichenberg *et al.* 2002; Zammit *et al.* 2004).

The present meta-analysis indicated that, by age 16, individuals who subsequently developed schizophrenia/SSD displayed poorer motor function than their peers who remained healthy. The lack of heterogeneity evidenced in this domain suggests that motor dysfunction is the most robust characteristic that distinguishes children/adolescents who subsequently develop schizophrenia. As noted previously, this is one of the most consistent findings in the literature on the antecedents of schizophrenia (Schenkel & Silverstein, 2004). Also consistent with these findings are the results of three studies that could not be included in the present meta-analysis of motor function because of lack of available data (Crow *et al.* 1995), or overlapping samples (Schiffman *et al.* 2004; Cannon *et al.* 2006). These studies all reported deficits in motor function among children/adolescents aged 7–13 years who developed schizophrenia/SSD in adulthood. However, one study (Walker *et al.* 1994) observed a reduction in motor dysfunction with increasing age among children who later developed schizophrenia, which may reflect the insensitivity of measures of motor function or age-related improvements in motor function similar to those reported among typically developing children. In addition, one prospective study of a birth cohort that repeatedly assessed children did not detect motor function deficits at every age among those who later developed schizophreniform disorder (Cannon *et al.* 2002). Given the relative paucity of prospective longitudinal studies that have assessed motor function through childhood and adolescence with repeated assessments, it is unclear whether motor dysfunction is present across all periods of development among individuals developing schizophrenia/SSD.

Whether or not children and adolescents developing schizophrenia/SSD do poorly in school is currently unclear. Two reviews found that repeating a school year and achieving poor grades were associated with an increased risk of developing SSD (MacCabe, 2008; Welham *et al.* 2009*a*). The results of the present meta-analyses indicated no significant difference in either overall academic achievement or performance on mathematics tests between individuals who did and did not later develop schizophrenia/SSD. This may be due, in part, to the inclusion of a study with a poorly matched comparison group (Ang & Tan, 2004). In that study, the individuals who subsequently developed psychosis showed deterioration in mathematics test scores from age 12 to age 16. In the present meta-analysis, all of the participants in the studies that assessed performance in mathematics were aged 11 or 12 years. Furthermore, a study excluded from the Mathematics domain due to age of participants also found significant differences in mathematics achievement between individuals aged 12–18 years who did and did not develop schizophrenia in adulthood (Watt & Lubensky, 1976). It is possible that individuals who later develop schizophrenia/SSD display a decline in performance on mathematics tests after age 12. Although significant heterogeneity was reported for both domains of academic performance, it could not be explored because of the limited number of studies meeting inclusion criteria. It is possible that the heterogeneity observed in the present meta-analysis and the inconsistent results across studies reflect differences in educational systems and measures of academic achievement that may preclude the examination of these domains in future meta-analyses.

Strengths and limitations

The present study is characterized by two principal strengths. One, the meta-analyses included only studies that had assessed performance in youth aged 16 years or younger. None of the 23 studies included in the meta-analyses reported that they had assessed prodromal symptoms at the same time as they assessed cognitive and/or motor performance. However, given the participants' age at the time of assessment, it is unlikely that the participants who subsequently developed schizophrenia/SSD had entered the prodromal phase of illness. Thus, the present results suggest that deficits in IQ and motor function emerge during childhood and early adolescence, prior to the onset of the prodrome. A second strength of the present meta-analyses was the examination of four domains of functioning: IQ, motor function, general academic achievement, and achievement in mathematics tests. Only the IQ domain had been examined previously using meta-analytic techniques. Despite using broad search terms to identify relevant studies, only 23 studies met final criteria for inclusion in the present meta-analyses. This was primarily due to the limited number of studies of cognitive and motor function in youth aged 16 years or younger who subsequently developed schizophrenia/SSD. More evidence is needed. Although the small number of

studies precluded the examination of the heterogeneity of results obtained in domains other than IQ, the strict criterion requiring that participants had been assessed by age 16 allowed us further understanding of the development of schizophrenia/SSD.

A potential caveat relates to the use of meta-analytic methods for comparisons of cognitive and motor function among children/adolescents of differing ages, which may fail to reflect the discontinuous nature of cognitive development (Harris, 1995). However, of the 23 studies included in the present meta-analyses, 18 assessed participants at 13 years or under, and only six studies examined participants with an age range of more than 3 years (Offord, 1974; Watt & Lubensky, 1976; Walker *et al.* 1994; Ott *et al.* 1998; Amminger *et al.* 2000; Sørensen *et al.* 2010). As only a few studies reported results separately for males and females, the meta-analyses could not contribute to the growing evidence on sex differences in the development of schizophrenia/SSD.

Conclusions

The meta-analyses provide evidence that among youth aged 16 years or younger, individuals who subsequently developed schizophrenia/SSD displayed lower IQ and poorer motor function than youth who did not develop illness. These results extend previous findings by showing that these deficits precede the onset of illness and of the prodrome. The results also endorse the view that schizophrenia, at least in part, represents a disorder of neurodevelopment. Stable cognitive and motor deficits in childhood and early adolescence are potential targets for interventions that may modulate illness development or reduce the extent of dysfunction present in individuals who develop schizophrenia/SSD.

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Declaration of Interest

All authors are affiliated with the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre (BRC) for Mental Health at the South London and Maudsley National Health Service (NHS) Foundation Trust and the Institute of Psychiatry, King's College London, UK.

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Appendix II

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Misperceptions of Facial Emotions Among Youth Aged 9–14 Years Who Present Multiple Antecedents of Schizophrenia

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Similar to adults with schizophrenia, youth at high risk for developing schizophrenia present difficulties in recognizing emotions in faces. These difficulties might index vulnerability for schizophrenia and play a role in the development of the illness. Facial emotion recognition (FER) impairments have been implicated in declining social functioning during the prodromal phase of illness and are thus a potential target for early intervention efforts. This study examined 9- to 14-year-old children: 34 children who presented a triad of well-replicated antecedents of schizophrenia (ASz), including motor and/or speech delays, clinically relevant internalizing and/or externalizing problems, and psychotic-like experiences (PLEs), and 34 typically developing (TD) children who presented none of these antecedents. An established FER task (ER40) was used to assess correct recognition of happy, sad, angry, fearful, and neutral expressions, and facial emotion misperception responses were made for each emotion type. Relative to TD children, ASz children presented an overall impairment in FER. Further, ASz children misattributed neutral expressions to face displaying other emotions and also more often mislabeled a neutral expression as sad compared with healthy peers. The inability to accurately discriminate subtle differences in facial emotion and the misinterpretation of neutral expressions as sad may contribute to the initiation and/or persistence of PLEs. Interventions that are effective in teaching adults to recognize emotions in faces could potentially benefit children presenting with antecedents of schizophrenia.

Key words: emotion recognition/high risk/child and adolescent psychopathology/social functioning/psychotic-like experiences

People with schizophrenia display a marked impairment in recognizing emotions in the faces of others, particularly anger, sadness, and fear, and less difficulty recognizing happy expressions.[1,2] Facial emotion recognition (FER) difficulties are associated with poor social functioning[3] and have implications for the development, course, and outcome of the disorder.[4] Yet, interventions to improve FER performance (eg, Training of Affect Recognition)[5] can reduce these deficits and elicit generalized improvement in other social cognitive domains.[6]

FER impairments are apparent not only among individuals with chronic schizophrenia (for review see Kohler et al 2010)[2] but also among individuals experiencing a first episode of psychosis[7,8] and among unaffected adolescent (though only for neutral facial expressions)[9] and adult first-degree relatives of individuals with schizophrenia.[10] Thus, abnormalities in FER are present at illness onset and may also index vulnerability for schizophrenia. Prospective studies following individuals at elevated risk for developing schizophrenia are needed to determine the extent to which impairments of FER precede illness and represent potential targets for early intervention. Among symptomatic, help-seeking individuals meeting ultra-high risk (UHR) criteria for psychosis,[7,8,11–13] evidence for FER impairments is mixed. Two studies reported FER impairments relative to healthy participants,[7,11] while another study indicated specific difficulties in correctly identifying neutral expressions.[13] A study of a large British birth cohort comprising 5267 children reported no association between FER at 8 years and subclinical psychotic symptoms at 12 years.[14] By contrast, a recent cross-sectional study of 748 children aged 10–13 years indicated that those reporting

psychotic-like experiences (PLEs) on questionnaires were poorer at recognizing facial emotional expressions, primarily sadness.[15] Unfortunately, as with many previous FER studies, no information was provided about the nature of the facial emotion misperceptions committed when processing facial expressions. Though PLEs in childhood are significantly associated with later psychotic illness,[16,17] they are also associated with an increased risk of anxiety disorders[16] and other psychiatric disorders including affective disorders, drug use disorders, and personality disorders,[18] albeit to a lesser extent. Thus, PLEs constitute a relatively nonspecific marker of risk for subsequent psychiatric disorders. Further, cross-sectional data from the general population indicate significant comorbidity of PLEs with emotional and behavioral problems,[19,20] implying that the observed relationship between PLEs and FER reported by Roddy et al[15] might reflect the presence of unreported internalizing and/or externalizing psychopathology.

To better characterize the nature of FER associated with schizophrenia, several studies have examined facial emotion misperceptions. Relative to healthy adults, individuals with schizophrenia more often mislabel negative emotions to faces displaying no or neutral expressions.[21,22] Adolescent relatives of individuals with schizophrenia, compared with adolescents from healthy families, also more often incorrectly label neutral expressions as displaying negative emotions, predominantly mislabeling them as sad.[9] Among individuals with schizophrenia, and individuals at high risk for psychosis,[23] functional imaging has revealed hyperactivation of the amygdala during the processing of neutral expressions, which could reflect emotional salience being assigned to neutral stimuli.[24] It has been suggested that the tendency to misinterpret neutral facial expressions as displaying emotion may contribute to the development of positive symptoms in schizophrenia.[23] Previous research indicates that facial emotion misperceptions might constitute the cognitive mechanism contributing to the social impairment that characterizes UHR samples[13] and is a critical component to understanding FER difficulties in samples at risk for schizophrenia.

Until recently, there has been no practical method for identifying children who are at elevated risk for schizophrenia. Despite the high heritability of schizophrenia, only approximately one-third of individuals with schizophrenia have a first- or second-degree relative with the illness. Consequently, a positive family history identifies only a subset of children who will develop the illness.[25] Prospective investigations of birth cohorts have demonstrated consistently that, by middle childhood, individuals who later developed schizophrenia presented delays in motor and language development; disturbances in social, emotional, and behavioral functioning; and PLEs.[17] Based on this evidence, we developed questionnaires, to be completed by children aged 9–12 years and their primary caregiver, to identify children who present a triad of these replicated antecedents of schizophrenia (ASz).[26,27] We defined ASz to include (1) early speech and/or motor developmental delays/abnormalities; (2) social, emotional, and/or behavioral problems in the clinical range; and (3) PLEs. It is thought that the identification of children who present multiple antecedents of schizophrenia that have been replicated in prospective longitudinal studies will offer greater sensitivity and specificity for later development of schizophrenia than any one antecedent.

We are currently following the development of ASz children to determine the specificity and sensitivity of the triad of antecedents for later schizophrenia development. We anticipate that some ASz children will develop schizophrenia and spectrum disorders, some will develop other disorders, and others will remain healthy. In the interim, our investigations have shown that ASz children, compared with typically developing (TD) children who present no antecedents and no family history of schizophrenia or a spectrum disorder, are characterized by features observed among adults with schizophrenia including (1) deficits in performance on standardized intelligence and neuropsychological tests of executive function and memory,[28] (2) dyskinetic movement abnormalities,[29] (3) reduction in the amplitude of the error-related negativity event-related potential component generated in the anterior cingulate that indexes internal monitoring of behavior,[30] and (4) structural brain abnormalities in the superior/middle temporal gyri.[31] Further, among children aged 9–12 years, two-thirds (69%) of those presenting with the triad of antecedents report distress and/or functional impairment associated with their PLEs.[27]

This study sought to determine whether ASz children present FER difficulties similar to those reported among individuals with schizophrenia and at-risk youth, after accounting for intelligence quotient (IQ) differences between ASz and TD groups,[28] which may contribute to FER performance. The study examined overall performance on FER tasks, as well as the specific nature of facial emotion misperceptions. We hypothesized that ASz children would be less accurate than TD children in identifying emotions in facial expressions and that they would more often mislabel neutral faces with other emotion expressions. In particular, we anticipated that ASz children would misidentify neutral expressions as sad, as was reported in a study of youth with family histories of schizophrenia using the same FER task.[9]

Method

Participants

Classrooms of children aged 9–14 years and their caregivers completed questionnaires to assess replicated antecedents of schizophrenia (see online supplementary material for further details). In brief, ASz children were defined as those presenting (1) a score in the clinical range

Table 1. Demographic and Intellectual Characteristics of Participants

	ASz (n = 34)		TD (n = 34)		
	n (%)		n (%)		Statistics
Proportion male	23 (68)		20 (59)		$\chi^2 = 0.6$, df = 1, $P = .5$
Ethnicity[a]	—		—		$\chi^2 = 3.5$, df = 3, $P = .3$
White British	9 (27)		12 (35)		—
White other	7 (19)		11 (32)		—
Black African; African Caribbean	9 (27)		7 (21)		—
Other	9 (27)		4 (12)		—
	Mean	SD	Mean	SD	
Age at facial emotion assessment	12 y, 1 m	17 m	12 y, 5 m	16 m	$t_{(66)} = -1.2$, $P = .2$
Mean time between completion of antecedent screening questionnaires and facial emotion assessment	23 m	14 m	28 m	14 m	$t_{(66)} = -1.5$, $P = .1$
IQ[b]	98.6	10.3	109.7	12.2	$t_{(66)} = -4.1$, $P < .001$

Note: ASz: presenting the triad of antecedents of schizophrenia; TD: presenting none of antecedents of schizophrenia or family history of the disorder; y: years; m: months.
[a]Ethnicity was assessed according to the UK Census ethnic categories defined by the Office of National Statistics 2001[48]; "Black African; African-Caribbean" included children of mixed white-black African Caribbean ethnicity; "Other" included children predominantly of mixed ethnicity.
[b]IQ estimated using Wechsler Abbreviated Scale of Intelligence.[38]

(top tenth percentile of UK population norms) on the child-reported emotional symptom scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problem scales of the Strengths and Difficulties Questionnaire (SDQ)[32]; (2) a child-reported "certainly-true" response on at least 1 of 9 PLE items assessing subclinical hallucination and delusion symptoms[26,33]; and (3) a caregiver report of a motor and/or speech delay and/or abnormality. TD children were defined as those meeting none of these 3 criteria and who, in addition, had no first-, second-, or third-degree relative with schizophrenia or a schizophrenia spectrum disorder, as assessed by the Family Interview for Genetic Studies[34] conducted with the child's caregiver.

Screening questionnaires were completed by 1504 children aged 9–12 years and their primary caregiver, who represented 19% of children attending 73 collaborating primary schools in Greater London, United Kingdom. Among these, 9.4% of children met criteria for ASz and 22.9% presented none of the 3 antecedents and were thereby defined as TD.[27] Approximately half of the families participating in questionnaire screening provided information, allowing us to recontact them for further research. Among families approached to participate in further research, 41% of ASz and 42% of TD families declined participation. There were no differences observed as to age, sex, ethnicity, and prevalence of ASz triad components among ASz and TD children who participated and ASz or TD children who did not take part, with 1 exception. The proportion of ASz children who completed the FER task who obtained SDQ scores for emotional problems in the clinical range was significantly smaller than that of the ASz children who did not participate in this study.

The sample included 34 ASz and 34 TD participants, the latter selected as the best individual matches to the ASz children on sex and ethnicity from among 44 TD children who completed the FER task. Five ASz children in this study had at least 1 second-degree relative with a family history of schizophrenia or a schizophrenia spectrum disorder. None of the children presented a diagnosis of autism or Asperger's disorder, neurological disorder, or learning difficulties (IQ < 70), or had ever taken antipsychotic medication. As presented in table 1, at the time of testing, ASz and TD children did not differ on age, proportion male, ethnicity, or length of time since initial assessment. ASz children were characterized by significantly lower IQ than TD children.

Children provided written assent, and caregivers provided written informed consent, for participation in the study. Ethical review of the study was provided by the Joint South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry Research Ethics Committee.

Measures

Facial Emotion Processing. FER was assessed using the Penn Emotion Recognition Task (ER40), a computerized task that requires participants to correctly recognize facial emotions. The ER40 has been used previously to study adults with chronic schizophrenia,[35] youth with a family history of schizophrenia or spectrum disorders,[9] adolescents reporting PLEs,[15] and, more recently, young adults experiencing high and low levels of nonclinical psychosis.[36] The ER40 comprises 40 color photographs of faces displaying happy, sad, angry, fearful, and neutral

facial expressions (8 photographs of each emotional expression). The photographs were balanced for the intensity of emotion expressed (mild or high), and the age, gender, and ethnicity of the faces. Each face was presented serially on a computer screen, in random order, with 5 response options displayed to the right of each photograph (ie, "happy," "sad," "angry," "fear," or "no emotion" [neutral]). For each photograph, participants were instructed to select the response that best described the displayed emotion, as quickly and as accurately as possible. Responses were selected by computer-mouse click. Each face was displayed until a response was recorded. Details of task construction and ratings have been reported previously.[37]

Dependent variables extracted from the task for analysis were (1) number of correct responses for each type of emotion expression and (2) number of misattribution and mislabeling responses made for each type of emotion.

Procedure

Eligible children and their primary caregivers were invited to participate in a research study that incorporated the ER40 task within a comprehensive battery of assessments including measures of biological, psychosocial, and neurocognitive functioning. The ER40 was administered by a trained researcher using standard instructions. Participants practiced the task to ensure understanding of instructions. Testing time was approximately 10 min.

Statistical Analyses

Comparisons of the ASz and TD children on age at time of FER assessment, time since initial assessment and group assignment, and IQ, assessed using the Wechsler Abbreviated Scale of Intelligence,[38] were made using independent *t* tests; group differences on sex and ethnicity were tested using chi-square analyses. IQ was entered as a covariate in all FER analyses.

Previous investigations have indicated that FER performance improves during childhood and adolescence.[39] Accordingly, we performed correlation analyses between each ER40 variable and age; parametric correlation analyses (Pearson coefficient) were conducted on normally distributed performance variables, and nonparametric correlation analyses (Spearman coefficient) were performed on nonnormally distributed performance variables. No significant associations between task performance variables and age were detected.

Correct Identification of Facial Emotions. To examine the accuracy of facial emotion expression identification, a 2-group (ASz, TD) by 5-emotion (happy, sad, angry, fearful, and neutral) repeated-measures ANCOVA adjusting for IQ was conducted on the number of correct responses recorded for each emotion.

Facial Emotion Misperceptions. Facial emotion misperceptions were examined by summing the total number of responses that (1) misattributed each emotion (eg, sadness) to faces expressing another emotion (eg, misattributing happy expressions-*as*-*sad*, angry expressions-*as*-*sad*, fearful expressions-*as*-*sad*, and neutral expressions-*as*-*sad* error types) and (2) incorrectly labeled each emotion (eg, mislabeling *angry*-*as*-happy expressions, *angry*-*as*-sad expressions, *angry*-*as*-fearful expressions, and *angry*-*as*-neutral expressions). For each of these 10 variables, proportions of total misperceptions were created by dividing these sums by the total number of incorrect responses possible (ie, 32) and multiplying by 100 to obtain a percentage for each misattribution and mislabeling misperception response type. Group differences were then explored using independent samples *t* tests for normally distributed proportions or Mann-Whitney *U* tests for nonnormally distributed proportions. Significant group effects were then further examined using repeated-measures ANCOVAs on the mean number of misattribution or mislabeling responses, with IQ as a covariate. The mean number of misattributions and mislabeling responses were not normally distributed, and a square root transformation was applied.[40]

For all ANCOVAs, follow-up simple main effects testing with Bonferroni adjustments for multiple comparisons were also conducted. Greenhouse-Geisser correction for repeated measures was employed for all but the mislabeling of emotions to face displaying anger and with estimates of effect size for each analysis reported.

Assessment of Triad Stability. FER assessments were completed, on average, 2 years after the initial identification of children using antecedent screening questionnaires. At the time of FER assessments, children completed the same questionnaires used to determine group assignments in order to reassess the 2 ASz triad components that could change over time. Of the 34 ASz children, 4 (12%) obtained scores on the SDQ psychopathology subscales in the "normal" range based on UK population norms, and they responded "not true" on all 9 PLE items. All ANCOVAs were repeated excluding these 4 children. As results were similar to those obtained with the complete sample who met ASz criteria at the initial community screening assessment, these analyses are presented in online supplementary material.

Associations With ASZ Components. Four multiple linear regression models were computed to explore associations of the components of the antecedent triad with the 4 facial emotion processing outcome variables on which ASz children performed significantly more poorly than TD peers: total correct facial emotion identifications, misattribution of neutral expressions to faces displaying other emotions, mislabeling of other emotions to faces displaying anger, and mislabeling of sadness to faces displaying neutral expressions. Each model included the

6 predictors assessing the triad components, total PLE score, total number of speech and/or motor delays or abnormalities, and scores for SDQ subscales assessing emotional problems, conduct problems, hyperactivity-inattention, and peer relationships problems.

Results

Table 2 presents means and standard deviations for correct responses by emotion type and for the 4 total emotion misperceptions (misattribution and mislabeling error) that showed statistically significant group differences. Cohen's *d* effect sizes indicating the magnitude of difference among groups (where an effect size of 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect)[41] and Bonferroni adjusted *P*-values are also indicated. Figure 1 illustrates the proportions of misidentifications of each emotion to faces displaying no emotion, separately for ASz and TD children.

Correct Identification of Facial Emotions

The 2-group (ASz, TD) by 5-facial emotion type (happy, sad, angry, fearful, neutral) ANCOVA on the number of correct responses, including IQ as a covariate, indicated a significant main effect of group [$F(1,65) = 8.5$, $P = .005$, $\eta p^2 = 0.12$], with TD correctly identifying more emotions than ASz. No significant main effect of emotion type [$F(3.1, 204.3) = 2.1$, $P = .09$, $\eta p^2 = 0.03$] or group-by-emotion interaction was detected [$F(3.1, 204.3) = 2.0$, $P = .11$, $\eta p^2 = 0.03$].

Facial Emotion Misperceptions

Among the 10 analyses conducted on the proportion of emotion misperception response types, 4 significant differences between ASz and TD were detected: (1) misattribution of sadness to faces displaying other emotion ($z = -1.9$, $P = .05$), (2) misattribution of neutral expressions to faces displaying other emotions ($z = -2.7$, $P = .007$), (3) mislabeling other emotions to faces displaying angry expressions ($z = -2.6$, $P = .01$), and (4) mislabeling other emotions to faces displaying neutral expressions ($z = -2.2$, $P = .02$).

Misattribution of Sadness to Faces Displaying Other Emotions

A 2-group (ASz, TD) by 4-facial expressions misattribution type (happy-as-sad, angry-as-sad, fear-as-sad, and neutral-as-sad) repeated-measures ANCOVA, including IQ as a covariate, indicated no main effect of group [$F(1,65) = 2.6$, $P = .11$, $\eta p^2 = 0.04$], no main effect of misattribution type [$F(2.1,136) = 0.63$, $P = .54$, $\eta p^2 = 0.01$], and no group-by-misattribution type interaction [$F(2.1, 136) = 2.4$, $P = .09$, $\eta p^2 = 0.04$].

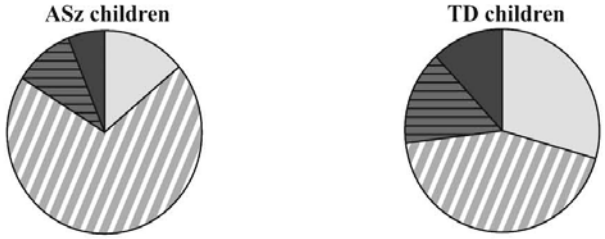
Misattribution of Neutral Expressions to Faces Displaying Other Emotions

A 2-group (ASz, TD) by 4-facial expression misattribution type (happy-as-neutral, sad-as-neutral, angry-as-neutral, and fear-as-neutral) repeated-measures ANCOVA, including IQ as a covariate, indicated a significant main effect of group [$F(1,65) = 7.6$, $P = .007$, $\eta p^2 = 0.11$] due to ASz misattributing neutral expressions to faces displaying other emotions relative to TD (ie, failing to detect emotion). No main effect of misattribution type [$F(2.8,185.5) = 0.50$, $P = .68$, $\eta p^2 = 0.008$] or group-by-misattribution type interaction was detected [$F(2.8, 185.5) = 1.2$, $P = .32$, $\eta p^2 = 0.02$].

Table 2. Comparisons of Performance on the ER40 Facial Emotion Recognition Task by ASz and TD Children

	ASz ($n = 34$)		TD ($n = 34$)		Effect Size
Performance Variable (Maximum Score Possible)	M	SD	M	SD	[b]*P*-value; Cohen's *d*
Mean number of total correct responses (40)	30.2	3.7	33.1	2.4	<.01; 0.9
Mean number of correct responses					
Happy expressions (8)	7.8	0.5	7.9	0.4	.37; 0.2
Sad expressions (8)	5.3	1.7	6.1	1.3	.05; 0.5
Angry expressions (8)	4.0	1.6	4.9	1.1	.02; 0.7
Fear expressions (8)	6.7	1.3	7.1	1.2	.81; 0.3
Neutral expressions (8)	6.4	1.9	7.2	1.2	.15; 0.3
Mean number of misperceptions[a]					
Other emotions misattributed as "Sad" expressions	2.5	2.3	1.4	1.5	.11; 0.6
Other emotions misattributed as "Neutral" expressions	3.9	2.2	2.5	1.4	<.01; 0.8
"Angry" expressions mislabeled as other emotions	4.0	1.6	3.0	1.1	.01; 0.7
"Neutral" expressions mislabeled as other emotions	1.7	1.9	0.8	1.2	.14; 0.6

[a]Face emotion misperceptions repeated-measures ANCOVAs were performed on square-root transformed data.
[b]Bonferroni adjusted *P*-values.



0.2 (14%)	Neutral-as-happy	0.2 (30%)
1.2 (70%)	Neutral-as-sad	0.4 (44%)
0.2 (10%)	Neutral-as-angry	0.1 (15%)
0.1 (6%)	Neutral-as-fear	0.1 (12%)
18%	Total percent for neutral	11%

Fig. 1. Proportions of other emotions mislabeled as neutral expressions.

Mislabeling of Other Emotions to Faces Displaying Angry Expressions

A 2-group (ASz, TD) by 4-mislabeling type (angry-as-happy, angry-as-sad, angry-as-fear, and angry-as-neutral) repeated-measures ANCOVA, including IQ as a covariate, was computed. Results indicated a significant main effect of group [$F(1,65) = 7.1$, $P = .01$, $\eta p^2 = 0.1$], with ASz more often mislabeling angry expressions as displaying other emotions relative to the TD. No main effect of misattribution type [$F(3,195) = 0.19$, $P = .90$, $\eta p^2 = 0.003$] or group-by-mislabeling type interaction was observed [$F(3,195) = 0.45$, $P = .72$, $\eta p^2 = 0.01$].

Mislabeling of Emotion to Faces Displaying No Emotion (Neutral Expressions)

A 2-group (ASz, TD) by 4-mislabeling (neutral-as-happy, neutral-as-sad, neutral-as-fear, and neutral-as-angry) repeated-measures ANCOVA, including IQ as a covariate, was conducted. Results indicated no main effect of group [$F(1,65) = 2.2$, $P = 0.14$, $\eta p^2 = 0.03$] or mislabeling type [$F(1.9,122.2) = 0.12$, $P = 0.88$, $\eta p^2 = 0.01$]. A significant group-by-mislabeling type interaction was detected [$F(1.9, 122.2) = 3.2$, $P = .05$, $\eta p^2 = 0.05$], with ASz significantly more often mislabeling neutral expressions as sad than TD ($P = .04$).

Associations With ASz Components

From all 4 regression models, only 1 significant relationship was detected: hyperactivity-inattention problems independently predicted mislabeling of sadness to faces with neutral expressions ($\beta = 0.10$, $t = -2.2$, $P = .04$).

Discussion

This study of FER extends our recent work characterizing dysfunctions among children presenting multiple, well-replicated antecedents of schizophrenia.[28–30] At the initial assessment, these children were younger than youth with a family history of schizophrenia or who met UHR criteria previously examined in FER investigations. As hypothesized, ASz children performed more poorly on FER than TD children after accounting for group differences in IQ. This finding is similar to that reported for older UHR samples.[8,11,13] These findings extend previous observations of FER impairments among adults with schizophrenia,[21] and individuals at risk for schizophrenia, in some[7,9,13,15,36] but not all[8,11,12] studies. In addition, ASz children, compared with TD children, misattributed faces displaying emotions as neutral expressions, and more often mislabeled neutral expressions as sad. Further, the examination of mislabeling of faces displaying anger indicated that ASz children had some difficulties identifying anger. Among ASz children, FER performance was not associated with specific components of the antecedent triad, with the exception that the score for hyperactivity-inattention problems independently predicted misattribution of sadness to faces with neutral expressions. Previous studies have not reported specific biases in FER task performance among adolescents with Attention Deficit Hyperactivity Disorder but indicate that these adolescents show random patterns of performance associated, perhaps, with impulsivity.[42] Thus, for the most part, the components of the triad of antecedents did not independently account for FER difficulties observed among ASz children. Rather, it was the

combination of all of the antecedents defining ASz that was associated with anomalies in FER task performance.

ASz children had difficulty correctly identifying angry facial expressions relative to TD children. However, among adults with schizophrenia and individuals with first-episode psychosis, pronounced difficulties are apparent in recognizing negative emotions such as anger, fear, and disgust.[8,21,22] An investigation of individuals who met UHR criteria, and who were approximately 3 years older than children in this study, reported difficulties only in recognizing fear and sadness.[11] More recently, a study of youth aged 10–13 years who reported PLEs observed difficulties identifying sadness in faces using a pencil and paper version of the ER40 task.[15] By contrast, trend level impairment in recognizing fear was reported among young adults with high levels of nonclinical psychosis relative to those experiencing low levels, using the well-validated computerized version of the ER40 task.[36] Inconsistent evidence for an impairment in recognition of negative facial emotion expressions among at-risk individuals suggests that these difficulties may become more apparent when FER skills are fully developed.[39]

Alternatively, inconsistencies in results of FER impairments across high-risk samples may result from differences in methodologies, including task design, emotion expressions that are assessed, and stimulus complexity.[43] In particular, the absence of neutral facial expressions in some FER paradigms is notable. Of the studies[9,11,13,15,36] that included neutral faces and reported differences in FER among individuals at high risk for schizophrenia relative to a healthy comparison group, 2 reported a specific impairment in the recognition of neutral facial expressions among the high-risk participants.[9,13] The studies that detected no difference in FER performance between at-risk and healthy individuals did not include neutral facial expressions in their FER paradigms.[8,12]

ASz children misattributed emotions to neutral expressions, and more often mislabeled a neutral expression as sad compared with healthy peers. It was not possible to explore potential interactions between emotion type and intensity of the expressions. Consequently, this study could not determine whether the response bias shown by ASz children reflected problems identifying emotions of low intensity in faces. Previously reported hyperactivation of the amygdala during processing of neutral expressions may explain, at least in part, the mislabeling of emotions to neutral expressions by ASz children, and, as suggested in previous reports of similar findings,[9,13,23,35] the result from this study is consistent with the notion that the development of schizophrenia involves the aberrant assignment of salience to insignificant stimuli.[44]

ASz children, by definition, present several of the known antecedents of schizophrenia including motor/speech abnormalities; PLEs; and social, emotional, and/or behavioral problems. Previous studies by our group have also shown that they present with dysfunctions characteristic of individuals with schizophrenia.[27] This study shows that these children also exhibit difficulty recognizing emotions in the faces of others, thereby lacking crucial information needed to guide their own behavior and to understand the behavior of others. It is plausible that the misinterpretation of facial emotions may contribute to the initiation of and/or persistence of PLEs. Indeed, previous research has indicated that difficulties in accurately perceiving emotion in the faces of others, particularly the mislabeling of neutral faces as negative expressions, contributes to some symptoms of schizophrenia such as delusion formation and suspicious thoughts.[45] It was not possible to determine the precise temporal association between the onset of PLEs and poor FER in this study. However, FER difficulties were observed in these children who continued to present the triad of ASz at time of FER assessment, approximately 2 years after the initial assessment. Thus, poor FER may be associated with persistent PLEs and social, emotional, and behavioral difficulties. Furthermore, difficulties with FER may also contribute to the poor social functioning observed among adults with schizophrenia,[1] to the declining social and role functioning that characterizes the prodromal period, and also to the premorbid social impairments reported among youth at high risk for schizophrenia.[17] Thus, interventions that have been shown to increase the accuracy of FER among adults with schizophrenia[5,6] could potentially benefit ASz children. This study has several limitations. The ER40 task output did not distinguish correct emotion responses by the 2 levels of emotional intensity displayed in the faces. Therefore, it is not clear whether the significant differences between ASz and TD children in mislabeling a neutral expression as sad or incorrectly identifying emotional expressions as neutral or sad occurred primarily in facial expressions of low intensity. In real-life social interactions, faces typically display subtle variations in emotional expressions. Further, FER difficulties observed among ASz children may also be due to basic face identification/perception deficits that were not examined. Deficits in face perception have been identified in some, but not all, studies of adults with schizophrenia[1] and may reflect impairments in memory and attention.[46,47] To date, only 1 study has included a task of face perception while investigating FER deficits among individuals at-risk for schizophrenia, and findings indicated no impairment.[13] Finally, this study was limited by a relatively small sample. Nonetheless, despite limited statistical power, the results consistently demonstrated that children who presented multiple antecedents of schizophrenia since late childhood presented FER difficulties compared with TD peers.

This study benefited from using a FER test that has been used widely in previous studies of schizophrenia and, importantly, incorporated neutral facial expressions.

This allowed for meaningful comparisons of results with some previous studies.[9,21,35,36] The study identified children characterized by multiple, well-replicated antecedents of schizophrenia. This strategy may capture a broader range of children at risk for schizophrenia than selecting children with a family history of illness and a smaller number with higher risk than studies using only 1 antecedent such as PLEs to select children. Only follow-up of children defined as presenting ASz will determine the specificity and sensitivity of this strategy for identifying children who will subsequently develop schizophrenia.

This study obtained evidence of impairments in FER abilities among children and adolescents who may be at elevated risk for developing schizophrenia in adulthood. The study provided further support for the accumulating evidence that misattributions of emotional facial expressions as neutral, and the identification of neutral expressions as sad, may represent early risk markers for later development of schizophrenia. These impairments may represent targets for preventive interventions, which may in turn facilitate generalized improvements in social and emotional functioning among individuals at risk for schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Appendix III

Questionnaire for children aged 9-12 years

Please follow along as the questions are read out to you. Each time we read an item, please think carefully about it before you answer. Please mark your answer in the box like this: ☑ Let's start with some easy ones to help you practice:

A. How old are you?	**9 years or younger** ə	**10 years** ə	**11 years** ə	**12 years or older** ə
B. Which are you?	**a Boy** ə	**a Girl** ə		

From now on, please mark the box for Not True, Somewhat True, or Certainly True. It would help us if you answered all the items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of how things have been for you *over the last six months*.

	Not True	**Somewhat True**	**Certainly True**
Example: I always wear a watch	ə	ə	ə
1. I try to be nice to other people. I care about their feelings	ə	ə	ə
2. I am restless. I cannot stay still for long	ə	ə	ə
3. I get a lot of headaches, stomach-aches, or sickness	ə	ə	ə
4. I usually share with others (food, games, pens, etc.)	ə	ə	ə
5. I get very angry and often lose my temper	ə	ə	ə
6. I am usually on my own. I generally play alone or keep to myself	ə	ə	ə
7. I usually do as I am told	ə	ə	ə
8. I worry a lot	ə	ə	ə
9. I am helpful if someone is hurt, upset, or feeling ill	ə	ə	ə
10. I am constantly fidgeting or squirming	ə	ə	ə

11. I have one good friend or more	ə	ə	ə
12. I fight a lot. I can make other people do what I want	ə	ə	ə
13. I am often unhappy, down-hearted, or tearful	ə	ə	ə
14. Other people my age generally like me	ə	ə	ə
15. I am easily distracted. I find it difficult to concentrate	ə	ə	ə
16. I am nervous in new situations. I easily lose confidence	ə	ə	ə
17. I am kind to younger children	ə	ə	ə
18. I am often accused of lying or cheating	ə	ə	ə
19. Often children or young people pick on me or bully me	ə	ə	ə
20. I often volunteer to help others (parents, teachers, children)	ə	ə	ə
21. I think before I do things	ə	ə	ə
22. I take things that are not mine from home, school, or elsewhere	ə	ə	ə
23. I get on better with adults than with people my own age	ə	ə	ə
24. I have many fears. I am easily scared	ə	ə	ə
25. I finish the work I am doing. My attention is good	ə	ə	ə

Well done! Just a few more questions to go!

The next items ask about thoughts or beliefs that you could have had *<u>at any time in your life</u>*, not just in the last six months. For each item, please mark the box for Not True, Somewhat True, or Certainly True. Remember to answer all the items as best you can even if you are not absolutely certain or the item seems daft!

	Not True	Somewhat True	Certainly True
1. Some people believe that their thoughts can be read. Have other people ever read your thoughts?	ə	ə	ə
2. Have you ever believed that you were being sent special messages through the television?	ə	ə	ə
3. Have you ever thought that you were being followed or spied upon?	ə	ə	ə
4. Have you ever heard voices that other people could not hear?	ə	ə	ə
5. Have you ever felt that you were under the control of some special power?	ə	ə	ə
6. Have you ever known what another person was thinking even though that person wasn't speaking?	ə	ə	ə
7. Have you ever felt as though your body had been changed in some way that you could not understand?	ə	ə	ə
8. Do you have any special powers that other people don't have?	ə	ə	ə
9. Have you ever seen something or someone that other people could not see?	ə	ə	ə
Has this happened in the last year?	ə	ə	ə

If you have had any of the experiences described above,

do these experiences upset you? ə No ə Yes

Do these experiences cause difficulties for you at home or

at school? ə No ə Yes

Have you had any of these experiences during the past year? ə No ə Yes

Please tell us today's date: _____

Please tell us your birthday (day and month): _____

In which year were you born? **1996:** ə **1997:** ə **1998:** ə **1999:** ə
2000: ə **2001:** ə

Is there anything else you would like to tell us about yourself?

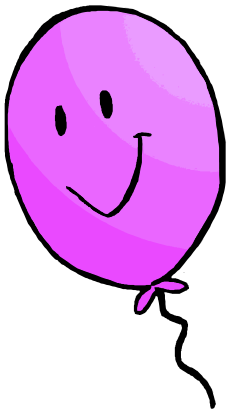
_____

_____

If you have any worries about the questions or your answers, and you would like to speak to a member of the research team, please contact:

Dr. Kristin Laurens (020)-7848-0964

THANK YOU VERY MUCH FOR YOUR HELP!!



Appendix IV

Caregiver Questionnaire

This form should be filled in by the child's main caregiver (usually, this is the child's mother or father).

It would help us if you answer all the questions as best you can, even if you are not absolutely certain of your answers or the questions don't seem to apply to your child.

Who is completing this form (e.g., child's Mother, Father, Grandmother, etc.)? : _____

Is your child (please mark the correct box, like this ☑): ə Male ə Female

When (date) and Where were these people born?:

Your child: D D / M M / Y Y Y Y. City: _____ ; Country _____

Child's mother: D D / M M / Y Y Y Y. City: _____ ; Country _____

Child's father: D D / M M / Y Y Y Y. City: _____ ; Country _____

Did your child ever live away from London? ə No ə Yes

Which ethnic background best describes your child? (please choose **one** of the following):

White: ə British ə Irish

ə Other White Background (specify):_____

Black or Black British: ə Caribbean ə African

ə Other Black Background (specify): _____

Asian or Asian British: ə Indian ə Pakistani ə Bangladeshi

ə Other Asian Background (specify): _____

Oriental or Oriental British: ə Chinese ə Japanese

ə Other Oriental Background (specify): _____

Mixed: ə White-Black Caribbean ə White-Black African ə White-Asian

ə Other Mixed Background (specify):_____

Other group not included above (specify): _____

If your child has any long-standing health problem or condition (e.g., diabetes, epilepsy,

etc.), please tell us what it is:

_____

Has your child, or any of your child's relatives, ever seen a doctor about a mental health condition? Please tell us **who** (e.g., child, or child's brother or sister, mum or dad, grandparent, cousin, etc.) and **which condition** (e.g., stress or anxiety or nerves, depression, psychosis or schizophrenia, inattention or hyperactivity, autism, eating disorder, etc.):

_____

The next questions ask about your child's speech and motor (physical) development. Some questions ask about things that may be hard to remember. Please try to answer as accurately as you can.

At what age did your child regularly use single words (not including 'mama' or 'dada') in a meaningful way?

ə before 1 year ə between 1-2 years ə 2-3 years ə 3-4 years ə 4 years or older ə don't know

At what age did your child regularly use two- and three-word phrases?

ə before 1 year ə between 1-2 years ə 2-3 years ə 3-4 years ə 4 years or older ə don't know

At what age was your child able to walk on his/her own?

ə by 6 months ə between 6-12 months ə 12-18 months ə 18-24 months ə 24 months or older ə don't know

In your child's first three years of life:

- Was there anything that seriously worried you about the way your child's speech developed?

- Were you ever seriously worried that your child was slow to reach his/her motor milestones

(e.g., to start standing / walking)?

Did you ever speak to a professional (e.g., speech therapist, health visitor, GP, etc.) about your concerns regarding your child's speech development?

Did your health visitor, GP, or other professional ever worry that your child was late:

- To stand on his/her own?

- To walk?

Does your child have any difficulty with co-ordination or unsteadiness (e.g., during activities such as playing sport, riding a bike, dancing etc.)

The next items ask about your child's Strengths and Difficulties. For each item, please mark the box for Not True, Somewhat True, or Certainly True. It would help us if you answered all the items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of your child's behaviour *over the last six months*.

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	ə	ə	ə
Restless, overactive, cannot stay still for long	ə	ə	ə
Often complains of headaches, stomach-aches, or sickness	ə	ə	ə
Shares readily with other children (treats, toys, pencils, etc.)	ə	ə	ə
Often has temper tantrums or hot tempers	ə	ə	ə
Rather solitary, tends to play alone	ə	ə	ə
Generally obedient, usually does what adults request	ə	ə	ə
Many worries, often seems worried	ə	ə	ə
Helpful if someone is hurt, upset, or feeling ill	ə	ə	ə
Constantly fidgeting or squirming	ə	ə	ə
Has at least one good friend	ə	ə	ə
Often fights with other children or bullies them	ə	ə	ə
Often unhappy, down-hearted, or tearful	ə	ə	ə
Generally liked by other children	ə	ə	ə
Easily distracted, concentration wanders	ə	ə	ə
Nervous or clingy in new situations, easily loses confidence	ə	ə	ə
Kind to younger children	ə	ə	ə
Often lies or cheats	ə	ə	ə
Picked on or bullied by other children	ə	ə	ə
Often volunteers to help others (parents, teachers, other children)	ə	ə	ə
Thinks things out before acting	ə	ə	ə

Steals from home, school or elsewhere	ə	ə	ə
Gets on better with adults than with other children	ə	ə	ə
Many fears, easily scared	ə	ə	ə
Sees tasks through to the end, good attention span	ə	ə	ə

Over the last six months, has your child had difficulties in one or more of the following areas: Emotions, concentration, behaviour, or being able to get along well with other people?

ə No ə Yes – minor difficulties ə Yes – definite difficulties ə Yes – severe difficulties

If you answered "Yes", please answer the following questions about these difficulties:

- Do the difficulties upset or distress your child?
  ə Not at all ə Only a little ə Quite a lot
- Do the difficulties interfere with your child's everyday life in the following areas?
  Home Life: ə Not at all ə Only a little ə Quite a lot
  Friendships: ə Not at all ə Only a little ə Quite a lot
  Classroom Learning: ə Not at all ə Only a little ə Quite a lot
  Leisure Activities: ə Not at all ə Only a little ə Quite a lot
- Do the difficulties put a burden on you or the family as a whole?
  ə Not at all ə Only a little ə Quite a lot

The next items ask about thoughts or beliefs that your child could have had at *any time* in his/her life, not just over the last six months. For each item, please mark the box for Not True, Somewhat True, or Certainly True. Remember to answer all the items as best you can even if you are not absolutely certain or the item seems daft!

	Not True	Somewhat True	Certainly True
Some people believe that their thoughts can be read. Has your child ever thought that other people could read his/her thoughts?	ə	ə	ə
Has your child ever believed that he/she was being sent special messages through the television or the radio, or that a programme had been arranged just for him/her alone?	ə	ə	ə
Has your child ever thought that he/she was being followed or spied upon?	ə	ə	ə
Has your child ever heard voices that other people couldn't hear?	ə	ə	ə
Has your child ever thought that he/she was under the control of some special power?	ə	ə	ə
Has your child ever claimed to know what another person was thinking even though that person wasn't speaking?	ə	ə	ə
Has your child ever thought his/her body had been changed in some way that he/she couldn't understand?	ə	ə	ə
Does your child have any special powers that other people don't have?	ə	ə	ə
Has your child ever seen something or someone that other people could not see?	ə	ə	ə
Has this happened in the last year?	ə	ə	ə
Have you ever seriously worried that your child was thinking or acting in a bizarre way?	ə	ə	ə

If 'Somewhat True' or 'Certainly True', please provide details:

_____

_____

If you answered "Somewhat True" or "Certainly True" to any of the questions on this page, please tell us whether these experiences have caused any difficulties for your child **over the past year**:

ə No ə Yes – minor difficulties ə Yes – definite difficulties ə Yes – severe difficulties

If you answered "Yes", please answer the following questions about these difficulties:

- Do the difficulties upset or distress your child?
  ə Not at all ə Only a little ə Quite a lot
- Do the difficulties interfere with your child's everyday life in the following areas?
  Home Life: ə Not at all ə Only a little ə Quite a lot
  Friendships: ə Not at all ə Only a little ə Quite a lot
  Classroom Learning: ə Not at all ə Only a little ə Quite a lot
  Leisure Activities: ə Not at all ə Only a little ə Quite a lot
- Do the difficulties put a burden on you or the family as a whole?
  ə Not at all ə Only a little ə Quite a lot

Please tell us today's date: D D / M M / Y Y Y Y

If you have any concerns about the questions you have been asked or about the answers you have given, and would like to speak to a member of the research team, please contact:

Dr. Kristin Laurens (020)-7848-0964
K.Laurens@iop.kcl.ac.uk

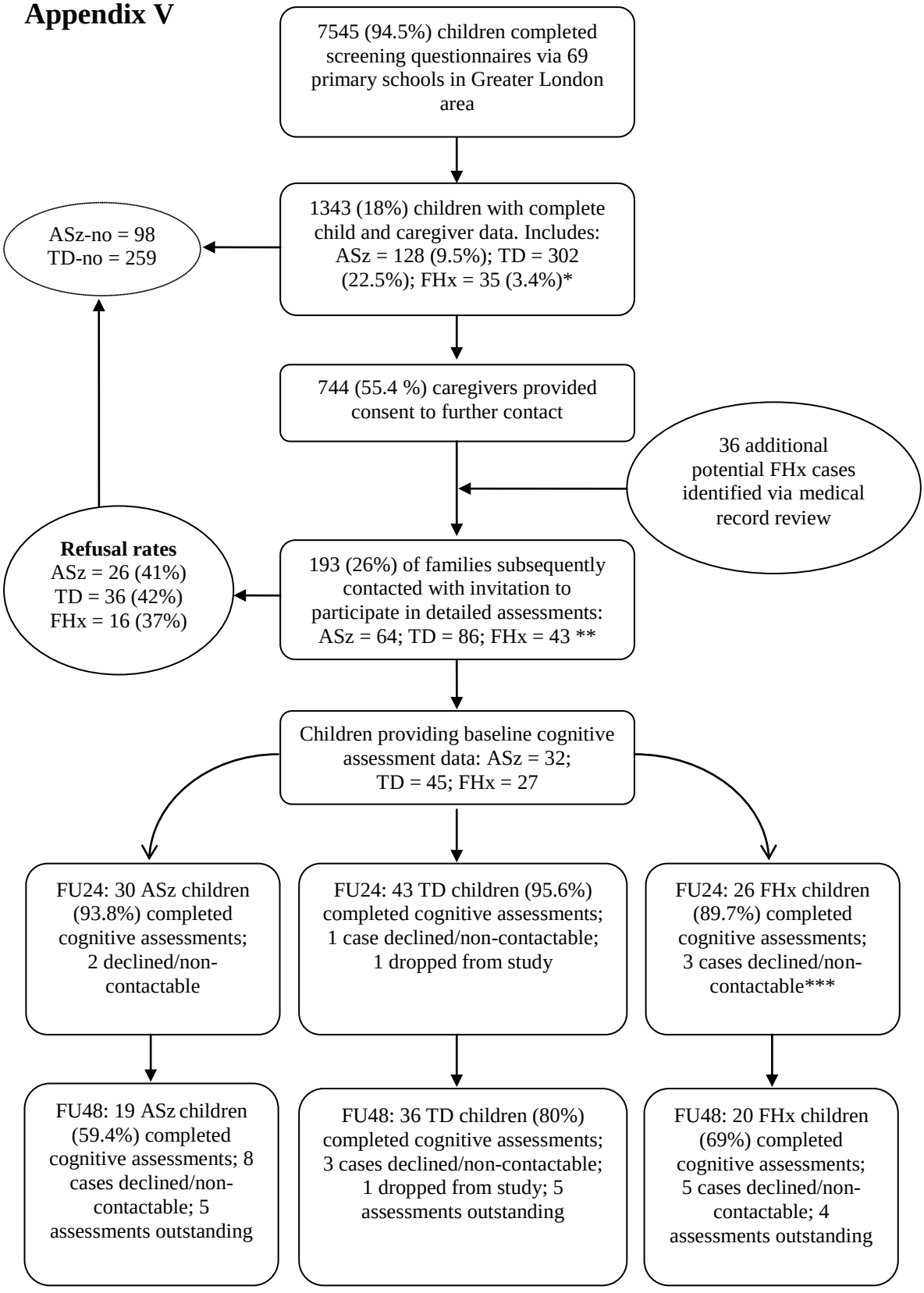
THANK YOU VERY MUCH FOR YOUR HELP!

DON'T FORGET TO FILL IN THE CONSENT FORM IF YOU WOULD LIKE TO PARTICIPATE

IN PART TWO OF THE RESEARCH

KING'S College LONDON
University of London

Appendix V



Notes. ASz status: all three antecedents; TD: none of the antecedents; FHx: reported family history of schizophrenia or schizoaffective disorder; ASz-no: all three antecedents present, but did not contribute data to thesis (see table six and seven); TD-no: none of antecedents present, but did not contribute data to thesis (see table six and eight of thesis); FU24: 24 month follow-up assessments; and FU48: 48 month follow-up assessments (assessments in this study phase were ongoing at the time of thesis submission).
* 1204 cases (family history of mental health problems questions not included in first wave of screening).
** Out of the 71 FHx potential cases identified, 28 FHx cases not contacted.
*** 2 additional children recruited at this study phase.